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(54) **DEVELOPMENT OF NOVEL CLOFARABINE ANALOGS FOR CANCER THERAPY**

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(51) **Int. Cl.**
C07H 19/16 (2006.01)
A61P 35/00 (2006.01)
C07H 19/20 (2006.01)

(52) **U.S. Cl.**
CPC **C07H 19/16** (2013.01); **A61P 35/00** (2018.01); **C07H 19/20** (2013.01)

(58) **Field of Classification Search**
CPC **C07H 19/16**; **C07H 19/20**; **A61P 35/00**
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,871,991 B2 1/2011 Boojamra et al.
8,633,168 B2 1/2014 Xiang et al.
10,981,944 B2 4/2021 Debien et al.
2020/0405629 A1 12/2020 Jaen et al.

FOREIGN PATENT DOCUMENTS

WO WO 2000/041531 7/2000
WO WO 10/2022
PCT/US2022/047890

OTHER PUBLICATIONS

Robak, T.; Robak, P., Purine Nucleoside Analogs in the Treatment of Rarer Chronic Lymphoid Leukemias. *Current Pharmaceutical Design*, 2012, 18, 3373-3388 (Year: 2012).*

Lubecka-Pietruszewska, K., et al. Clofarabine, a novel adenosine analogue, reactivates DNA methylation-silenced tumour suppressor genes and inhibits cell growth in breast cancer cells. *European Journal of Pharmacology*. 723, 2014, 276-287. (Year: 2014).*

Chrominski, M., et al. Synthesis of Trifluoromethylated Purine Ribonucleotides and Their Evaluation as 19F NMR Probes. *J. Org. Chem.* 2020, 85, 3440-3453. (Year: 2020).*

Alexander et al., (Acyloxy)alkyl carbamates as novel bioreversible prodrugs for amines: increased permeation through biological membranes, *J. Med. Chem.* 1988, 31, 318.

Almarasson, O., et al., Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines?, *The Royal Society of Chemistry*, 1889-1896, 2004.

Crews et al., Interim comparison of a continuous infusion versus a short daily infusion of cytarabine given in combination with cladribine for pediatric acute myeloid leukemia, (2002) *J Clin Oncol* 20: 4217-4224.

Ellion, G. G., The purine path to chemotherapy, (1989) *Science* 244: 41-47.

Genini et al., Deoxyadenosine analogs induce programmed cell death in chronic lymphocytic leukemia cells by damaging the DNA and by directly affecting the mitochondria, (2000) *Blood* 96: 3537-3543.

Grant, S., Ara-C: cellular and molecular pharmacology, (1998) *Adv Cancer Res* 72: 197-233.

Grem et al., Antimetabolites, (1999) *Cancer Chemother Biol Response Modif* 18: 1-38.

Heidelberger et al., Fluorinated pyrimidines and their nucleosides, (1983) *Adv Enzymol Relat Areas Mol Biol* 54: 58-119.

Huang et al., High molecular weight DNA fragmentation: a critical event in nucleoside analogue-induced apoptosis in leukemia cells, (1995) *Clin Cancer Res.* 1: 1005-1013.

Johnson, S. A., Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies, (2000) *Clin Pharmacokinet* 39: 5-26.

Plunkett, et al., Gemcitabine: metabolism, mechanisms of action, and self-potential, (1995) *Semin Oncol* 22(Suppl 11): 3-10.

Pott-Hoeck and Hiddemann, Purine analogs in the treatment of low-grade lymphomas and chronic lymphocytic leukemias, (1995) *Ann Oncol* 6: 421-433.

Warrell and Berman, Phase I and II study of fludarabine phosphate in leukemia: therapeutic efficacy with delayed central nervous system toxicity, (1986) *J Clin Oncol* 4: 74-79.

U.S. Appl. No. 63/272,147, filed Oct. 26, 2021, Omar Moukha-Chafiq.

Faderi et al. (2002) "New nucleoside analogues in clinical development," *Cancer Chemother Biol Response Modif* 20: 37-58.

(Continued)

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(57) **ABSTRACT**

The present disclosure is concerned with Clofarabine analogs for the treatment of various cancers such as, for example, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas). This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

3 Claims, 2 Drawing Sheets

(56)

References Cited

OTHER PUBLICATIONS

Faderl et al. (2005) "The role of clofarabine in hematologic and solid malignancies—development of a next-generation nucleoside analog," *Cancer* 103(10): 1985-1995.

Lodewyck (2012) "Clofarabine in clinical haematology," *Belgian Journal of Hematology* 3(1): 17-22.

* cited by examiner

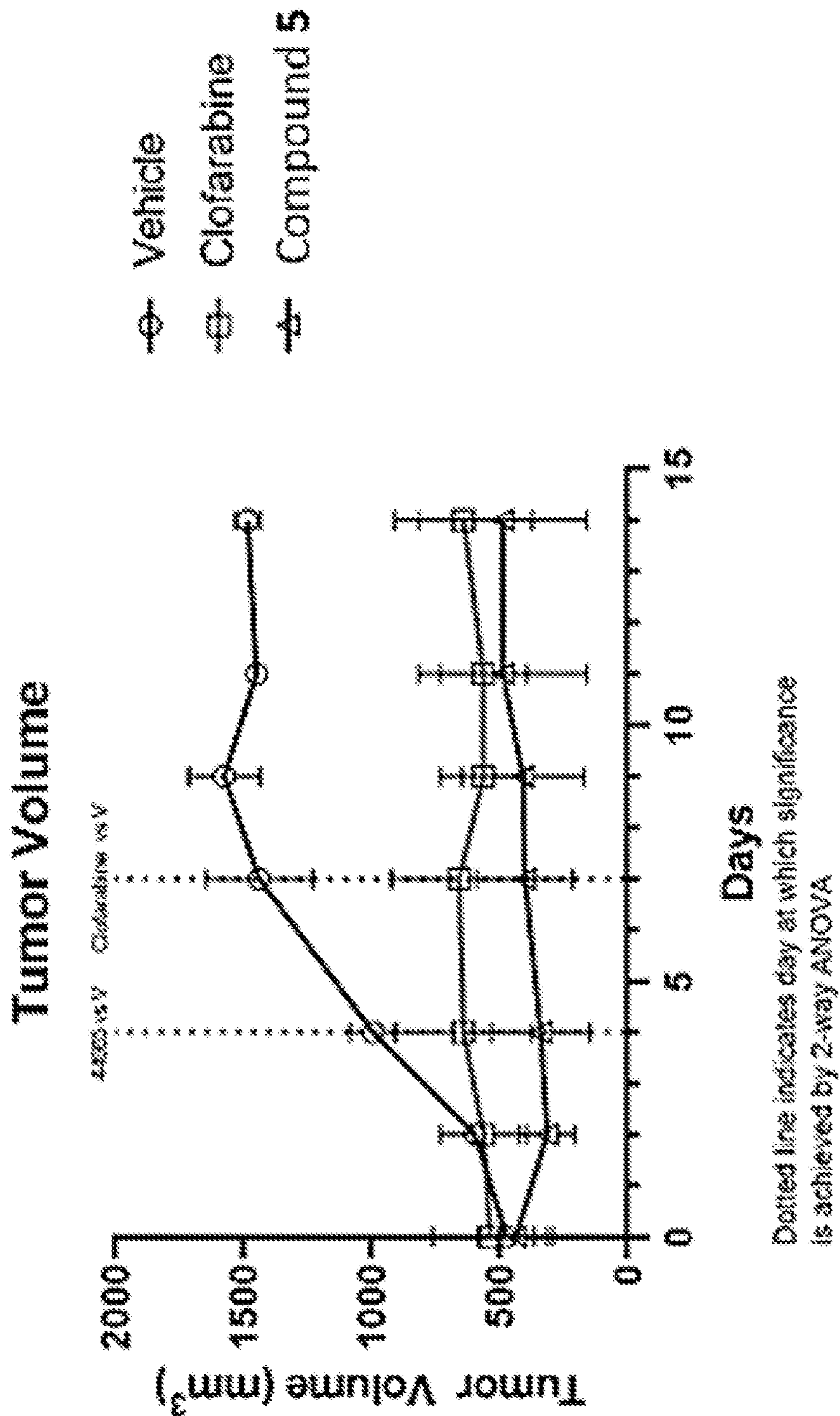


FIG. 1

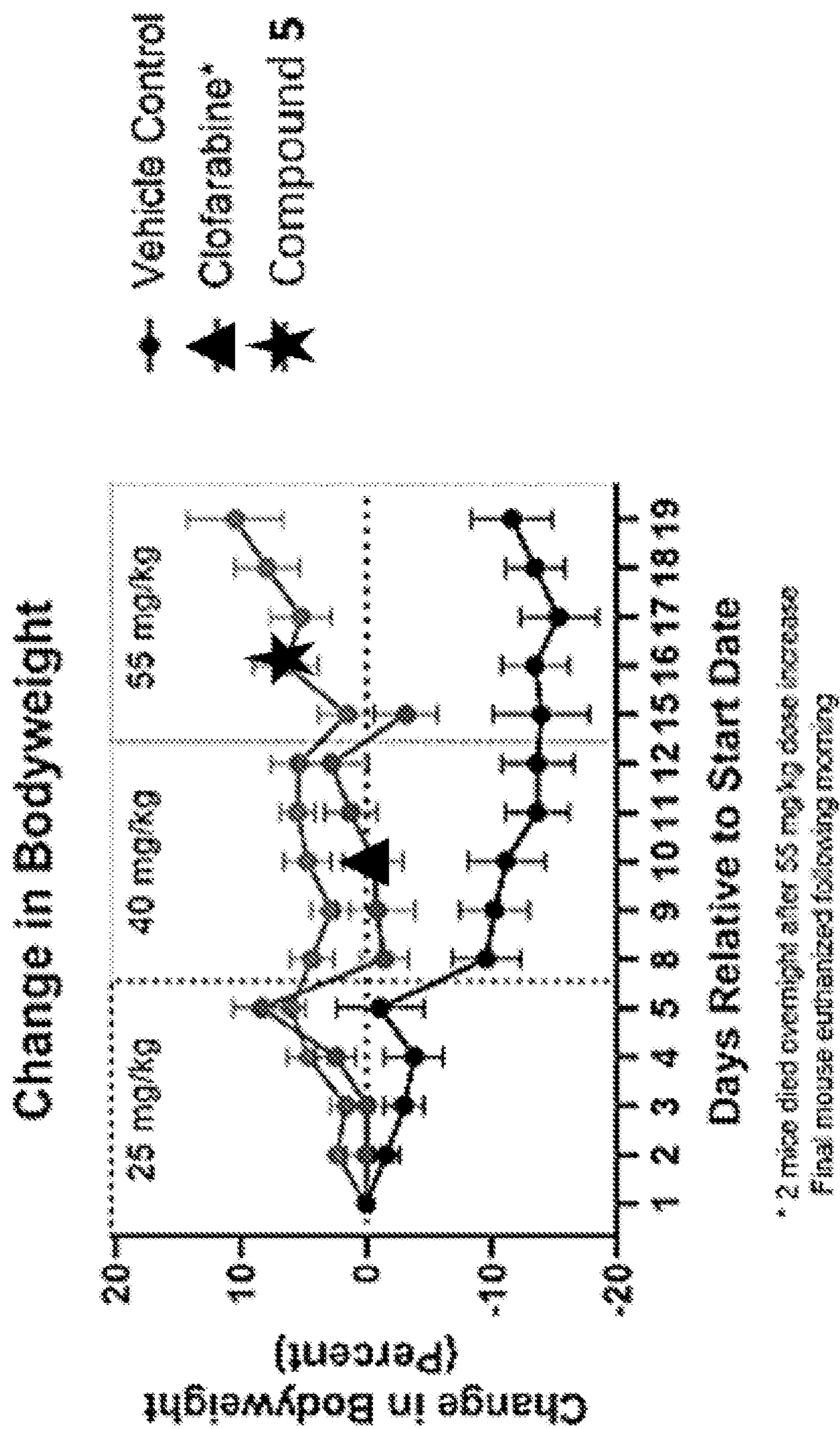


FIG. 2

**DEVELOPMENT OF NOVEL CLOFARABINE
ANALOGS FOR CANCER THERAPY**

CROSS-REFERENCE TO RELATED
APPLICATIONS

This application claims the benefit of U.S. Application No. 63/272,147, filed on Oct. 26, 2021, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND

The biology of tumor cells is comprised of a network of complicated processes that disrupt multiple layers of a cell's regulatory and survival pathways, eventually altering transcription of a variety of target genes. However intricate these processes, the capacity to synthesize DNA remains a vital feature of tumor cells. Proliferating cells, therefore, require a constant pool of purine and pyrimidine nucleotides to replicate; interference with their metabolism will lead to cell death.

Since their introduction in the 1960s, nucleoside analogs have become some of the most prevalent and active components of antitumor therapy (Ellion, G. G. (1989) *Science* 244: 41-47; Heidelberger et al. (1983) *Adv Enzymol Relat Areas Mol Biol* 54: 58-119). Nucleoside analogs disrupt nucleotide metabolism in one of two major ways: (1) incorporation into DNA and (2) inhibition of ribonucleotide reductase (RnR), an enzyme involved in the recycling of the cellular nucleotide pool. The combined effect of the analogs leads to termination of DNA chain elongation, inhibition of DNA synthesis, interference with DNA repair mechanisms, and apoptosis as the most likely final pathway of activity (Huang et al. (1995) *Clin Cancer Res.* 1: 1005-1013; Grem et al. (1999) *Cancer Chemother Biol Response Modif* 18: 1-38; Genini et al. (2000) *Blood* 96: 3537-3543; Johnson, S. A. (2000) *Clin Pharmacokinet* 39: 5-26). An intriguing aspect of nucleoside analogs is how apparently minor alterations in structure can result in major differences with respect to pharmacology, metabolism, and spectrum of activity (Faderi et al. (2002) *Cancer Chemother Biol Response Modif* 20: 37-58). The activity of cytarabine (1- β -D-arabinosylcytosine [ara-C]), a deoxycytidine analog, is restricted almost exclusively to acute myeloid leukemias (AML); whereas gemcitabine (2',2'-difluorodeoxycytidine), another carbohydrate-modified analog of deoxycytidine, has a therapeutic spectrum that has been expanded into solid tumor malignancies (Grant, S. (1998) *Adv Cancer Res* 72: 197-233; Plunkett, et al. (1995) *Semin Oncol* 22(Suppl 11): 3-10). Fludarabine (9- β -D-arabinofuranosyl-2-fluoroadenine 5'-monophosphate) and cladribine (2-chlorodeoxyadenosine [2-CdA]) have been among the first clinically useful purine nucleoside analogs (Pott-Hoeck and Hiddemann (1995) *Ann Oncol* 6: 421-433). Both are highly active in indolent lymphoproliferative disorders. Cladribine is inactive in adult AML but has shown efficacy in children with AML. Fludarabine is active in adult AML, but only at high doses, resulting in severe neurotoxicity (Warrell and Berman (1986) *J Clin Oncol* 4: 74-79; Crews et al. (2002) *J Clin Oncol* 20: 4217-4224).

Clofarabine (2-chloro-2'-fluoro-2'-deoxy-9- β -D-arabinofuranosyladenine) has provided an impressive example of how new nucleoside analogs can contribute to an understanding of alternative metabolic pathways and mechanisms

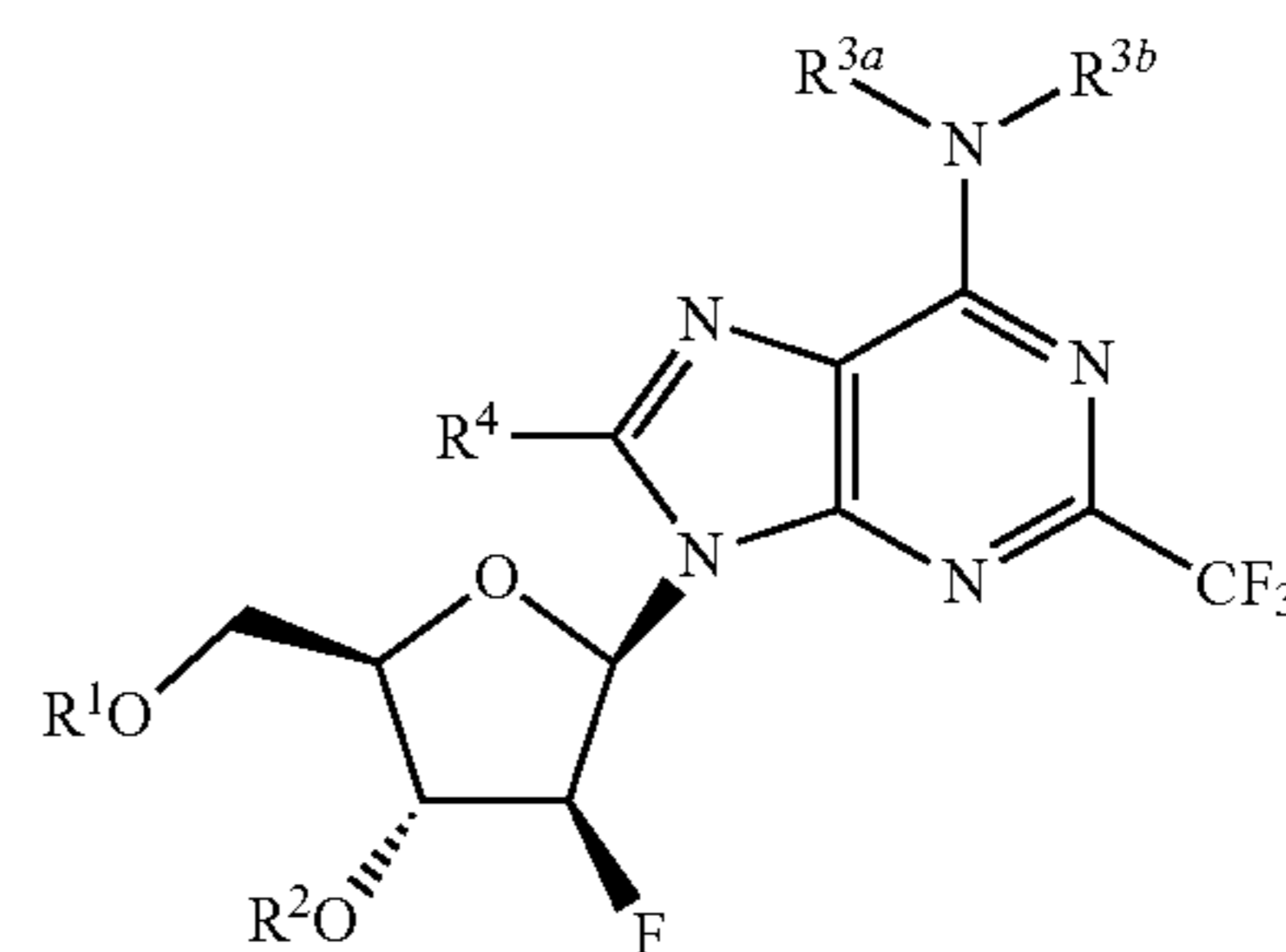
of action that may clarify as yet unexplained features of nucleosides with regard to the relation between structure, pharmacology, and activity. It is a next-generation deoxyadenosine analog that was synthesized as a rational extension of the experience with fludarabine and cladribine. Minor modifications in structure, such as halogenation at the 2-adenine and 2' positions of the carbohydrate, resulted in clofarabine retaining the mechanistically favorable properties of both previous agents: potent inhibition of DNA polymerases and of RnR. Clofarabine has shown antitumor activity in preclinical models and in clinical trials. The current emphasis of clofarabine lies in the acute leukemias, but its activity in other disease groups is being investigated actively.

In view of the foregoing, clofarabine represents not only a structural hybrid between fludarabine and cladribine, but also a functional hybrid combining the mechanistically favorable properties of both congener compounds with regard to inhibition of DNA polymerases and RnR. As such, clofarabine provides a promising scaffold for subsequent modifications to improve on the potency, cytotoxicity, and bioavailability, while exploiting the favorable mechanistic properties. Thus, there remains a need for clofarabine analogs and methods of making and using same.

SUMMARY

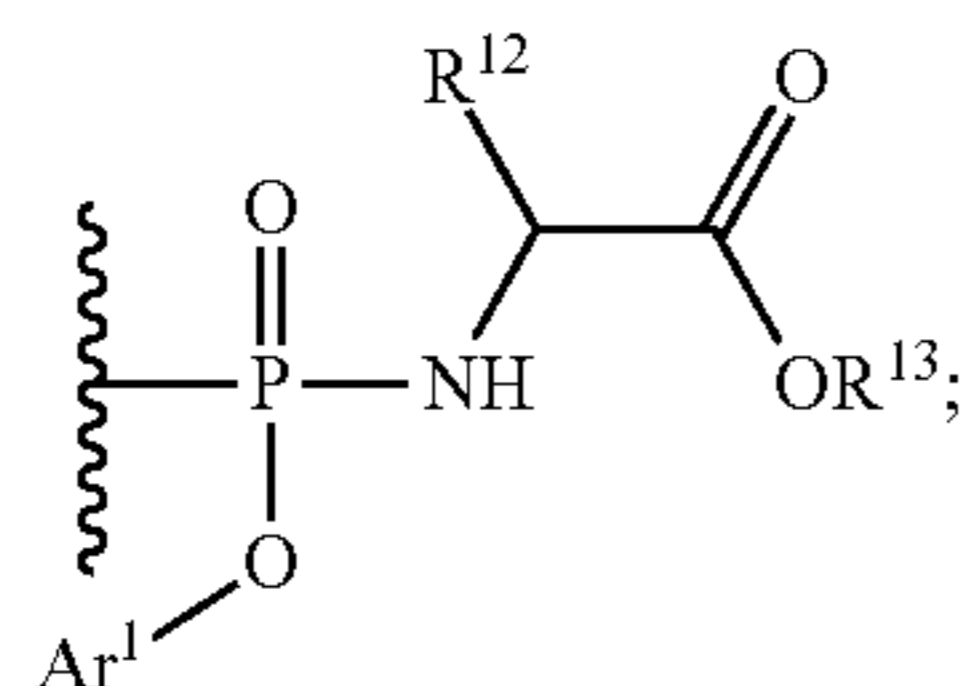
In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in one aspect, relates to compounds and compositions for use in the prevention and treatment of disorders of uncontrolled cellular proliferation such as, for example, cancers including, but not limited to, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

Thus, disclosed are compounds having a structure represented by a formula:



wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:

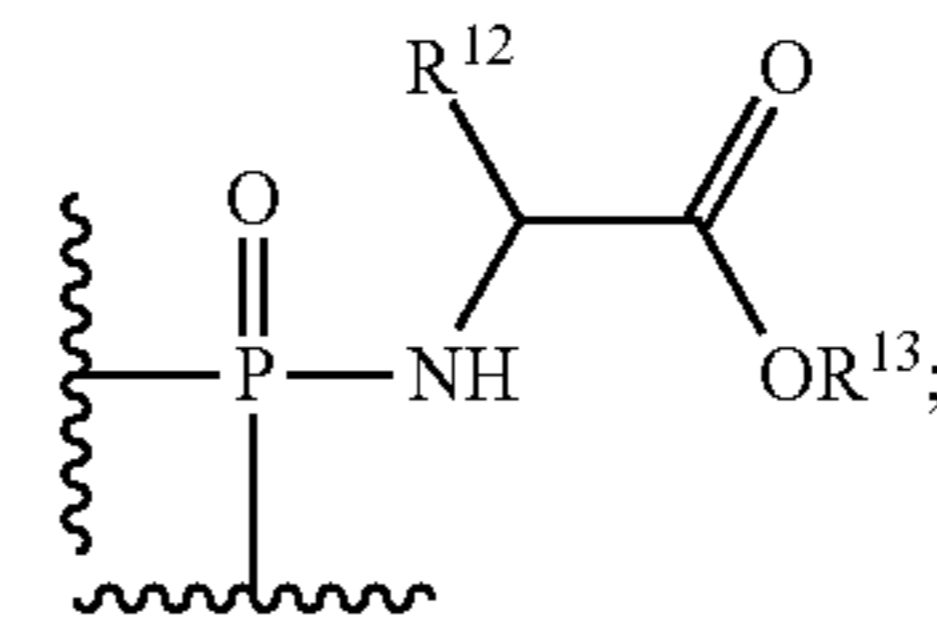
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wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)\text{R}^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8 alkyl})\text{CO}_2\text{H}$, $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^1 , and $-(\text{C1-C8 alkyl})\text{Cy}^1$; wherein Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkyl})$, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkylthiol})$, $-(\text{C1-C10 alkyl})\text{S}-\text{S}-(\text{C1-C10 alkyl})$, and Ar^2 ; wherein Ar^2 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloal-

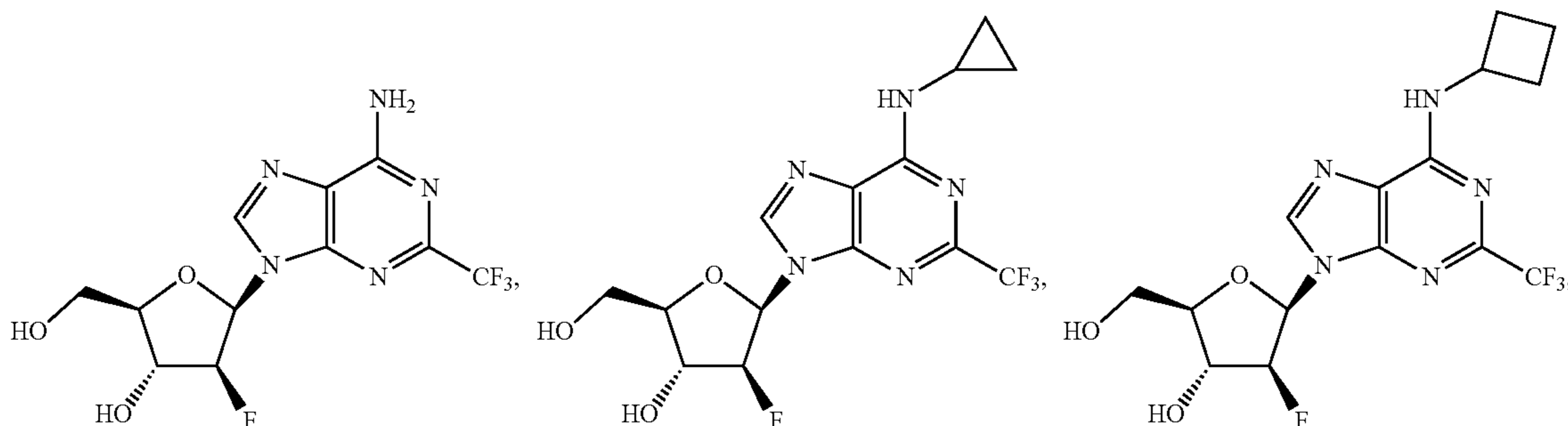
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alkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:

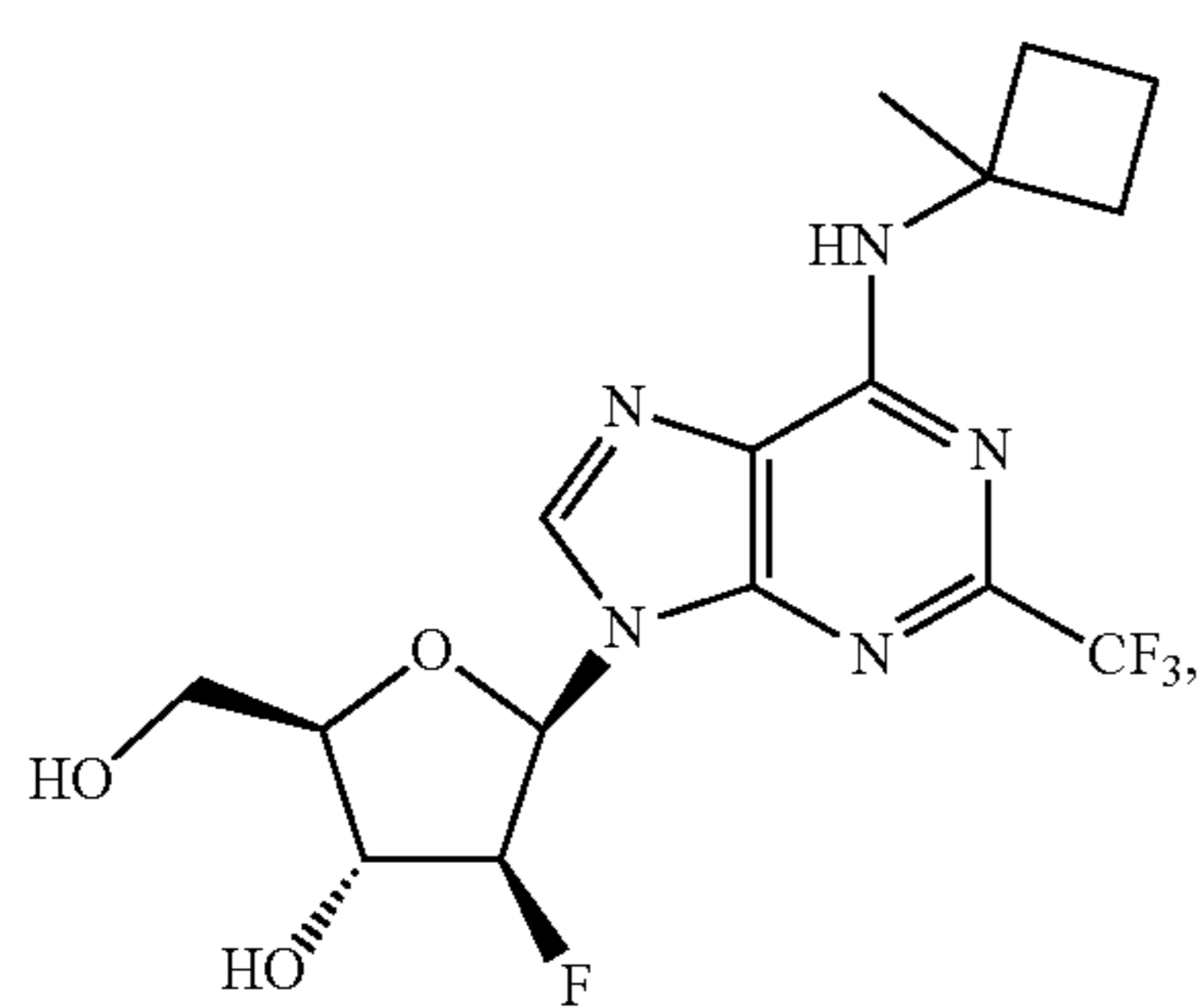


wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-\text{OH}$, C1-C12 alkyl, C1-C12 alkoxy, $-\text{C}(\text{O})\text{R}^{14}$, $-(\text{C1-C12 alkyl})\text{CO}_2\text{H}$, and $-(\text{C1-C6 alkyl})\text{Cy}^2$, provided that R^{3a} and R^{3b} are not simultaneously hydrogen; wherein R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)\text{R}^{21}$; wherein R^{21} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8 alkyl})\text{CO}_2\text{H}$, $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^3 , and $-(\text{C1-C8 alkyl})\text{Cy}^3$; wherein Cy^3 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy^2 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine, provided that when each of R^1 and R^2 is hydrogen, then at least one of R^{3a} and R^{3b} is a non-hydrogen group, and provided that when one of R^{3a} and R^{3b} is $-(\text{C1-C6 alkyl})\text{Cy}^2$, then R^1 is hydrogen, or a pharmaceutically acceptable salt thereof.

Also disclosed are compounds having a structure selected from:

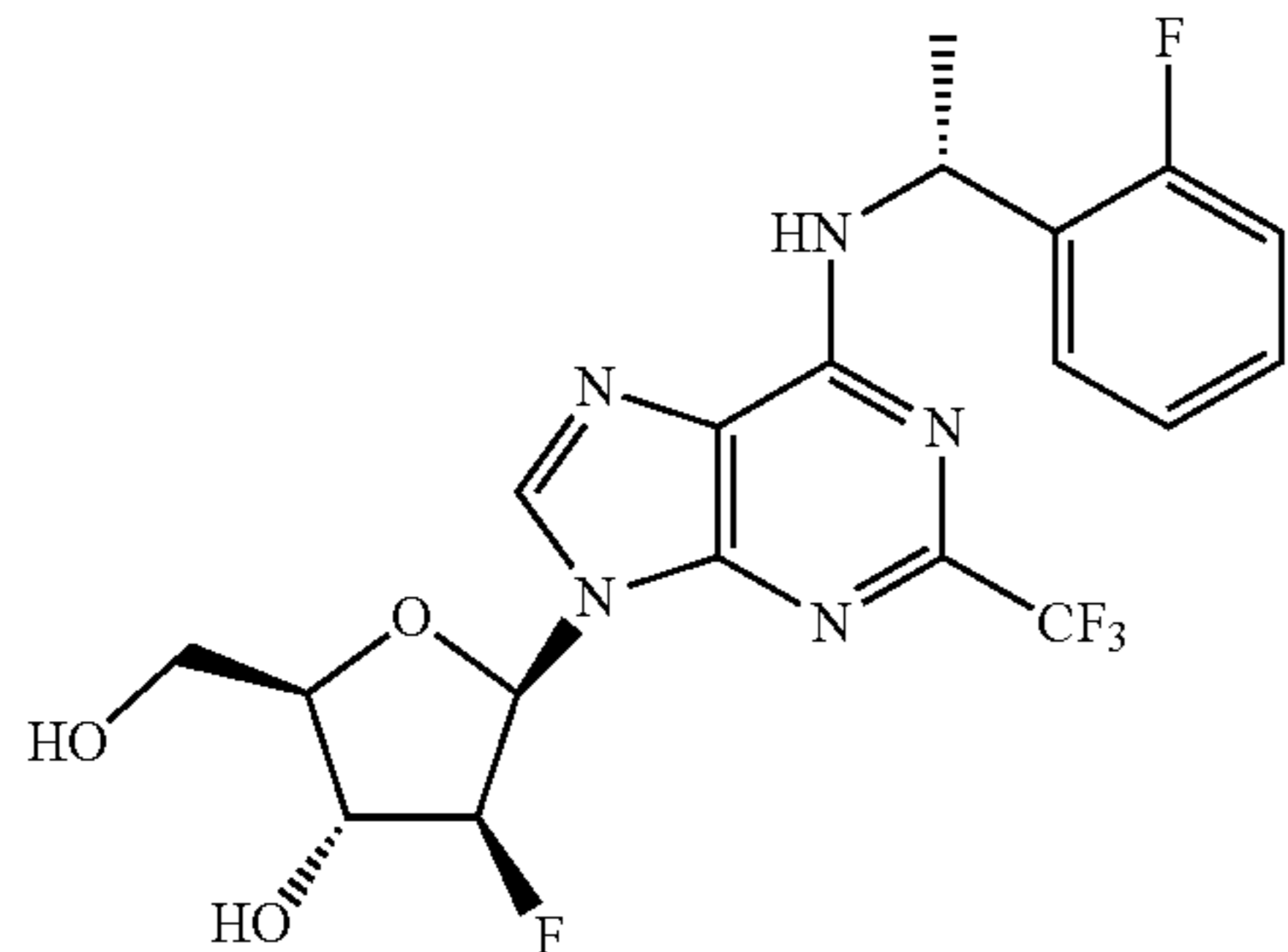
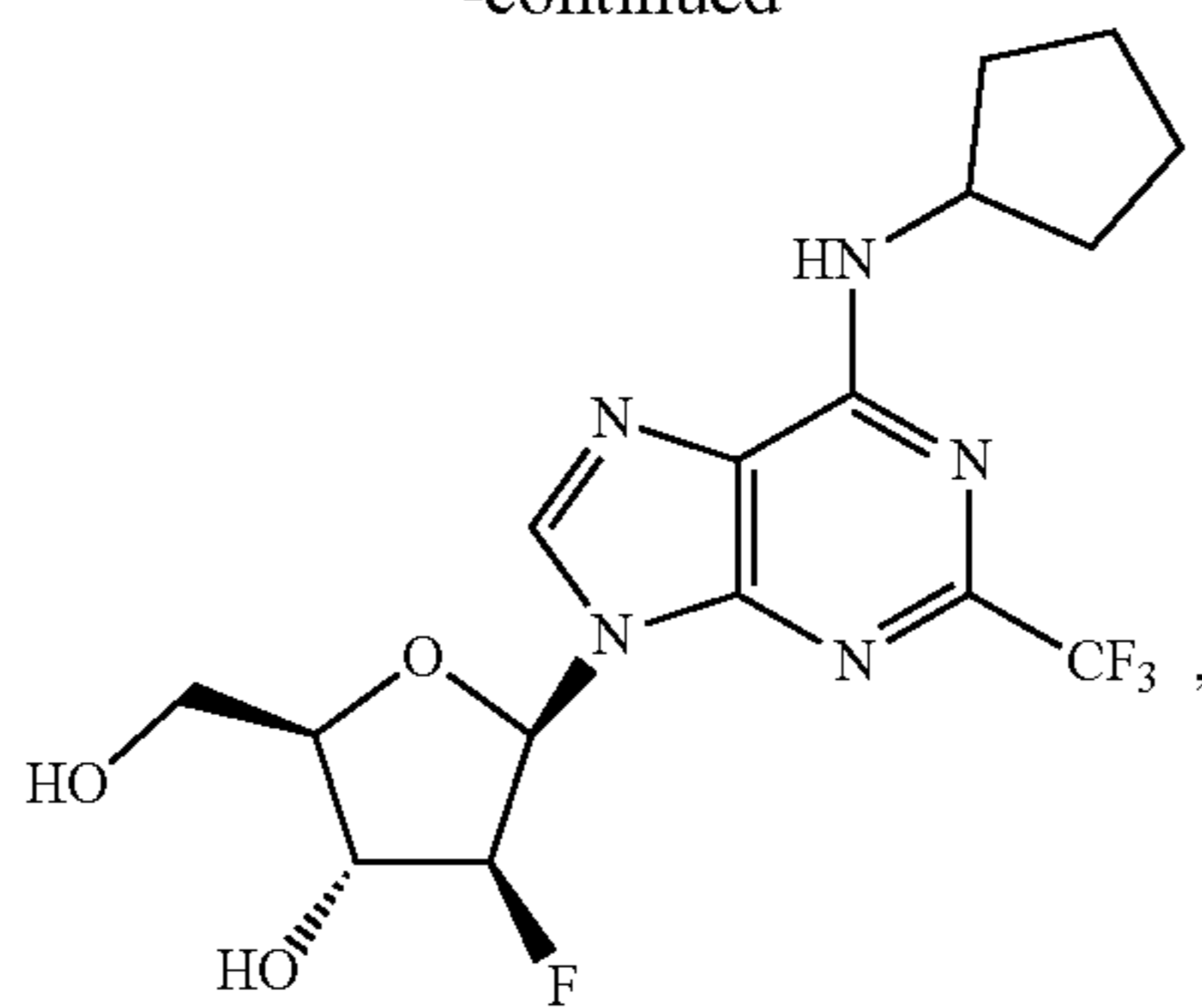


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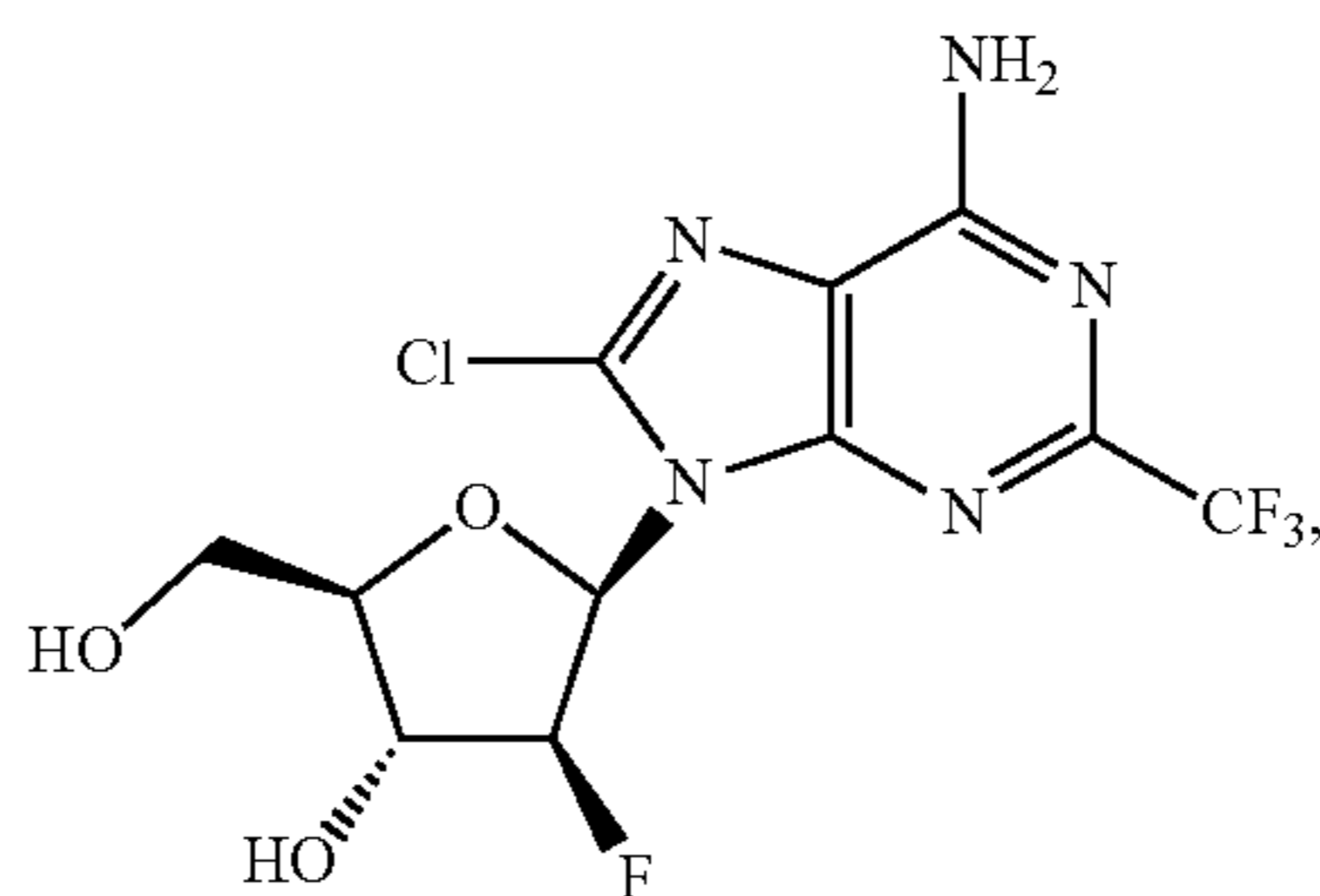


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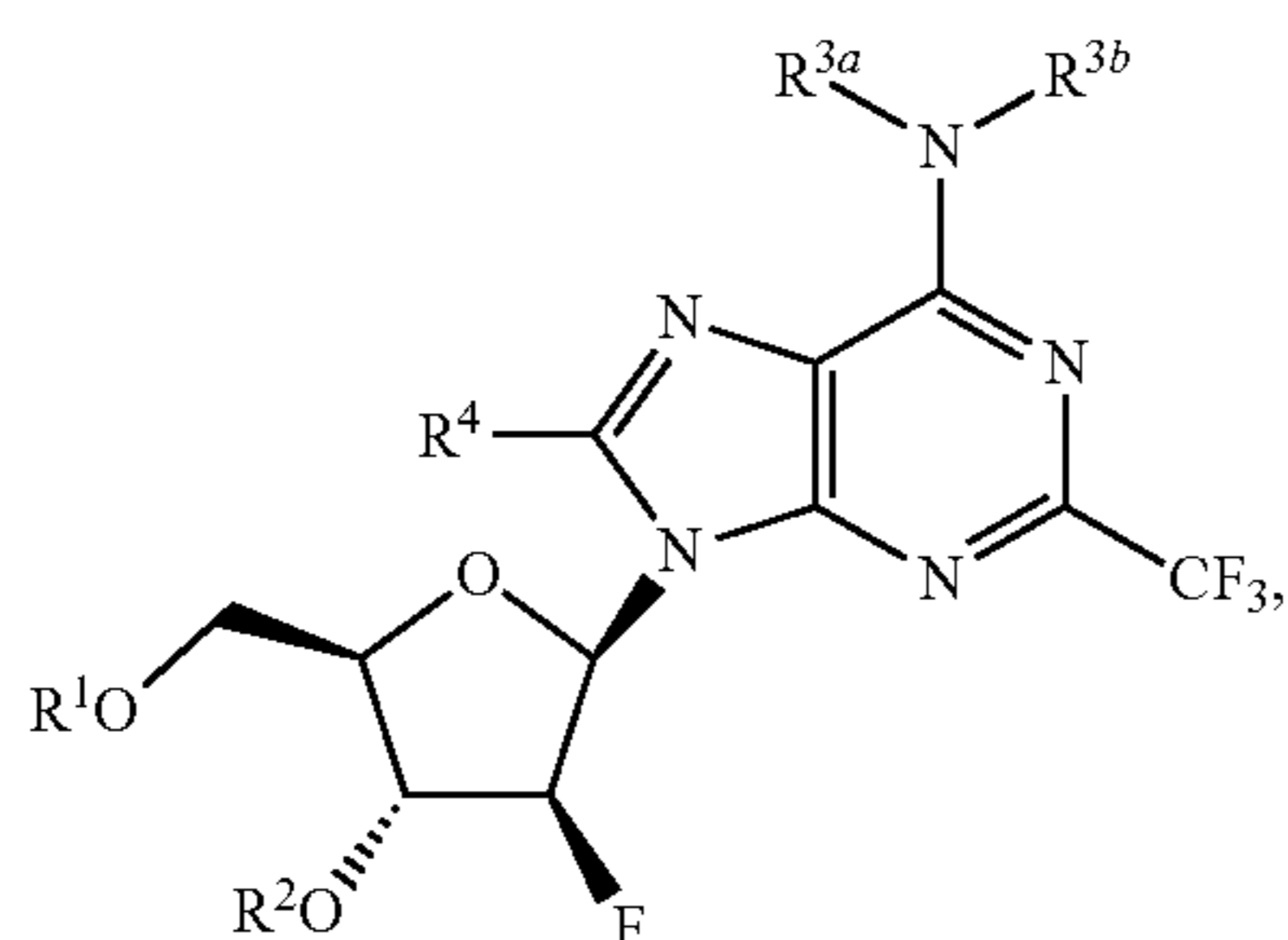
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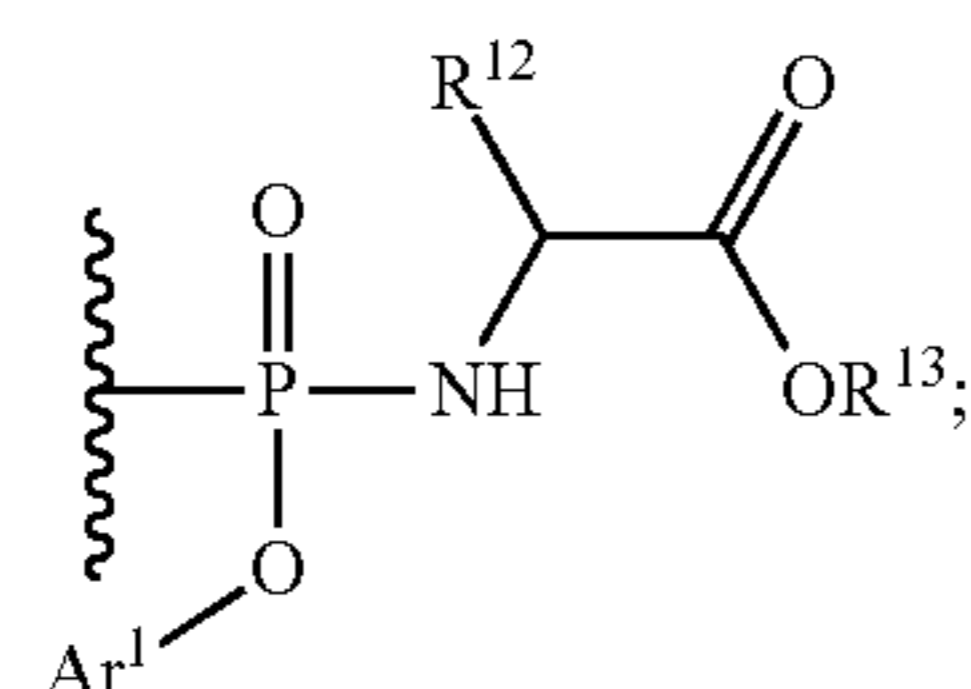
or a pharmaceutically acceptable salt thereof.

Also disclosed are pharmaceutical compositions comprising a therapeutically effective amount of a disclosed compound, and a pharmaceutically acceptable carrier.

Also disclosed are methods of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound having a structure represented by a formula:



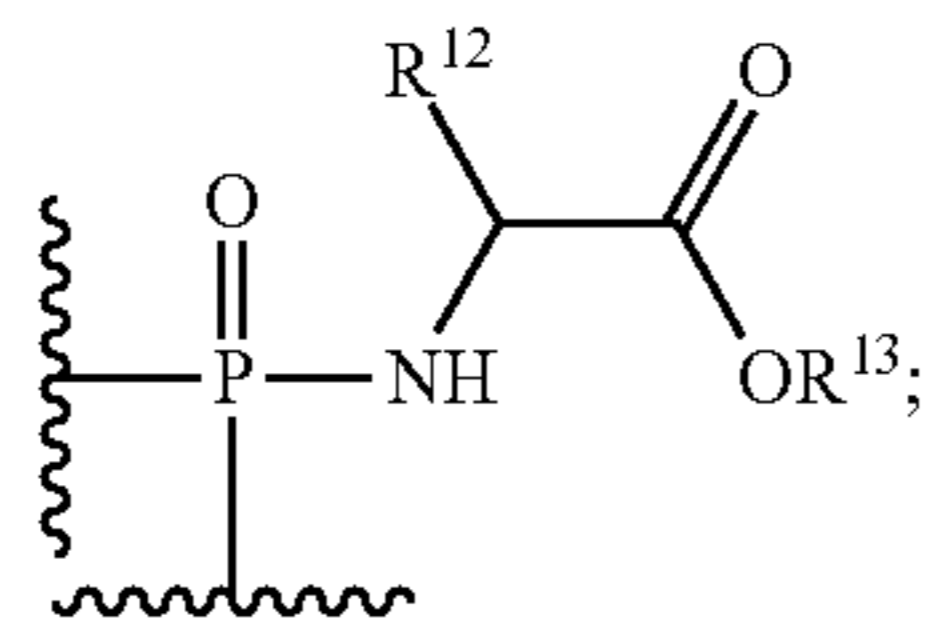
wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:



wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)\text{R}^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8}$

alkyl) CO_2H , $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^1 , and $-(\text{C1-C8 alkyl})\text{Cy}^1$; wherein Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkyl})$, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkylthiol})$, $-(\text{C1-C10 alkyl})\text{-S-S-}(\text{C1-C10 alkyl})$, and Ar^2 ; wherein Ar^2 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:

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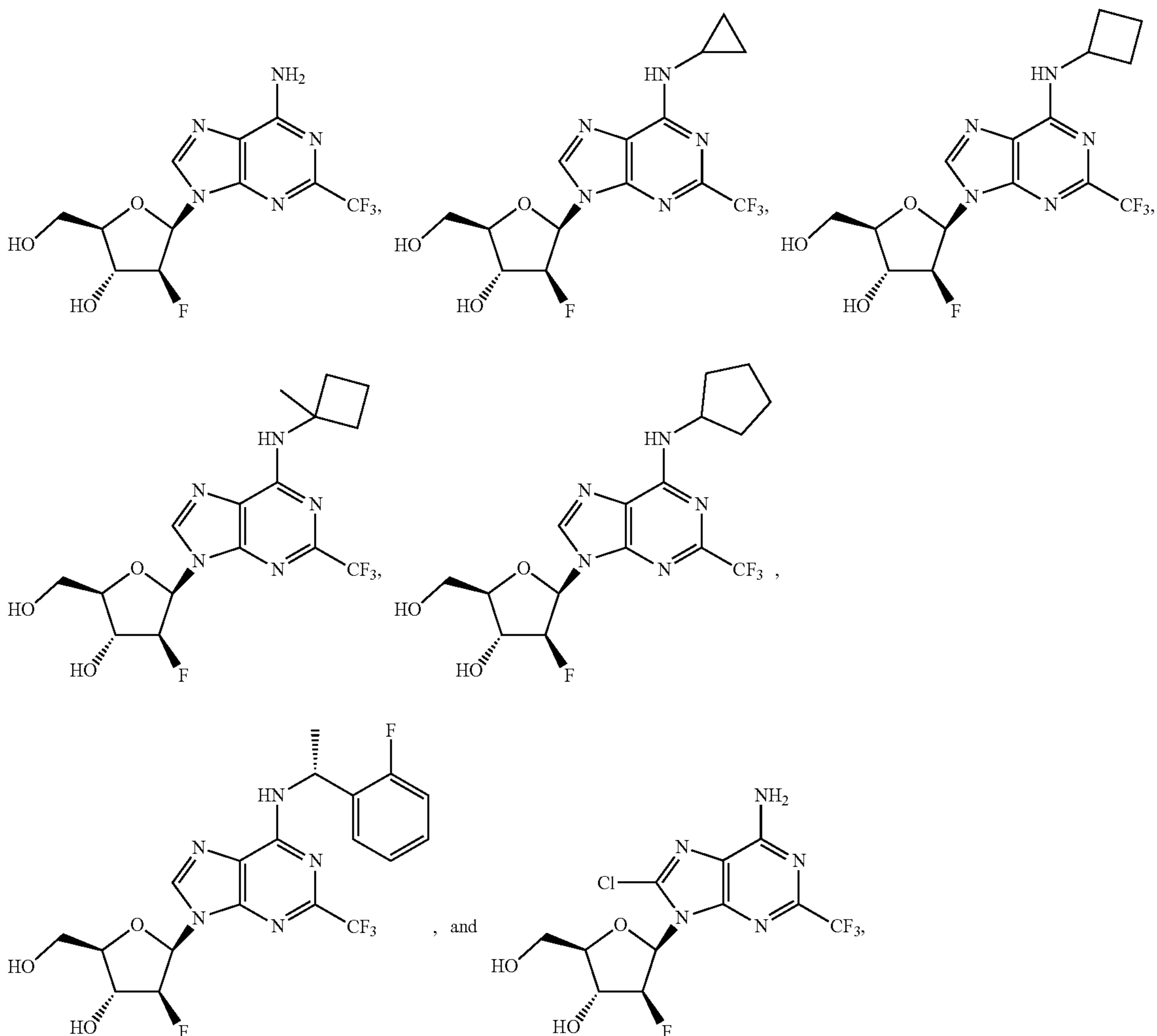


wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, C1-C12 alkyl, C1-C12 alkoxy, —C(O) R^{14} , —(C1-C12 alkyl)CO₂H, and —(C1-C6 alkyl)Cy²; wherein R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH₂)R²¹; wherein R^{21} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, —(C1-C8 alkyl)NHC(NH)NH₂, —(C1-C8 alkyl)CO₂H, —(C1-C8 alkyl)C(O)NH₂, Cy³, and —(C1-C8 alkyl)Cy³; wherein Cy³, when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl,

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when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine, provided that when each of R^1 , R^2 , R^{3a} , and R^{3b} are not simultaneously hydrogen, and provided that when each of R^1 , R^2 , and R^{3a} is hydrogen then R^{3b} is not —CH₂(unsubstituted cyclohexyl), or a pharmaceutically acceptable salt thereof, thereby treating cancer in the subject.

Also disclosed are methods of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound having a structure selected from:

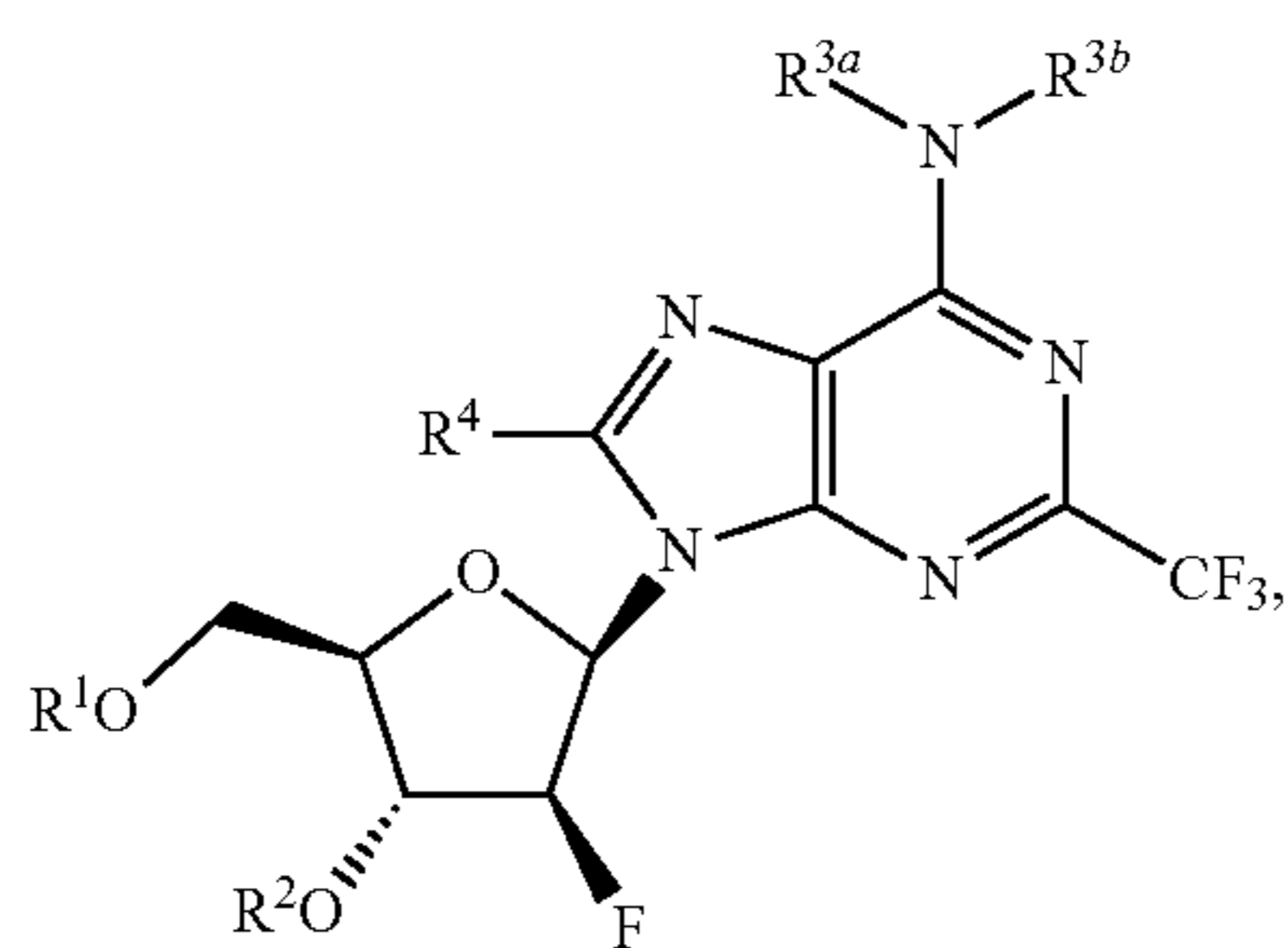


and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy²,

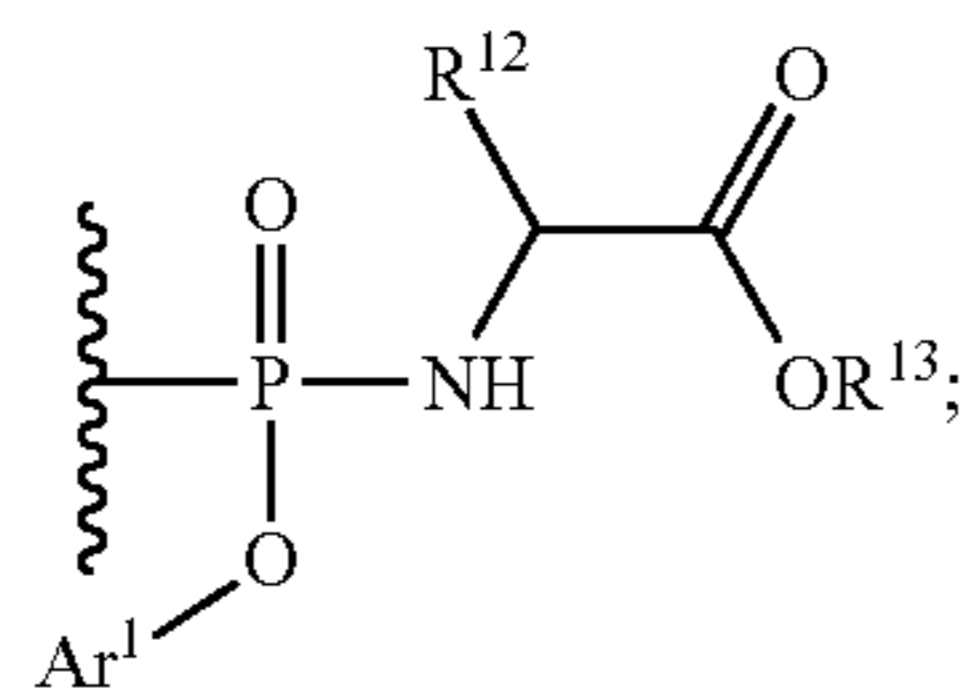
or a pharmaceutically acceptable salt thereof, thereby treating cancer in the subject.

Also disclosed are methods of modifying nucleic acid synthesis in a subject, the method comprising administering to the subject an effective amount of a compound having a structure represented by a formula:

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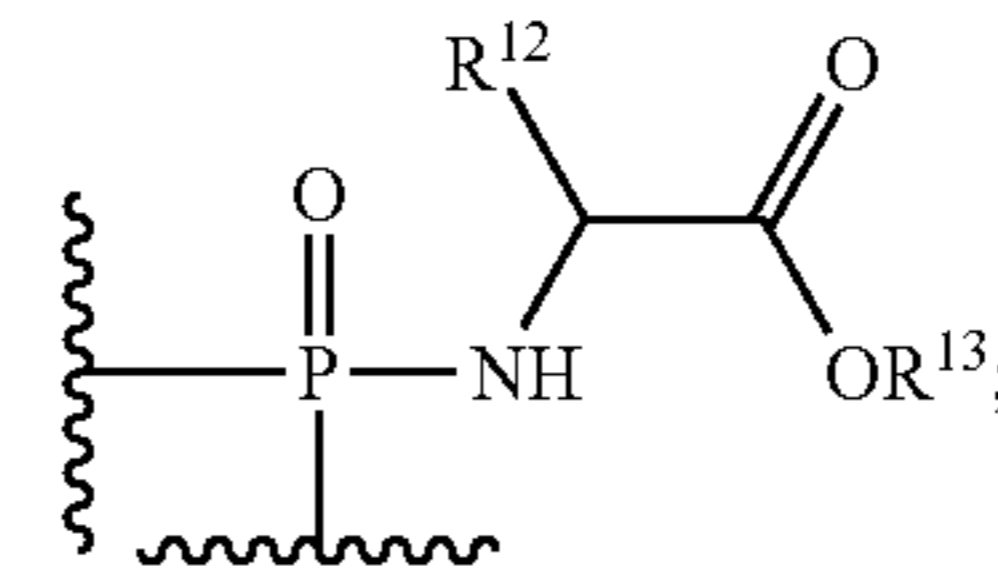
wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:



wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)R^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8 alkyl})\text{CO}_2\text{H}$, $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^1 , and $-(\text{C1-C8 alkyl})\text{Cy}^1$; wherein Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkyl})$, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkylthiol})$, $-(\text{C1-C10 alkyl})\text{S}-\text{S}-(\text{C1-C10 alkyl})$, and Ar^2 ; wherein Ar^2 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$,

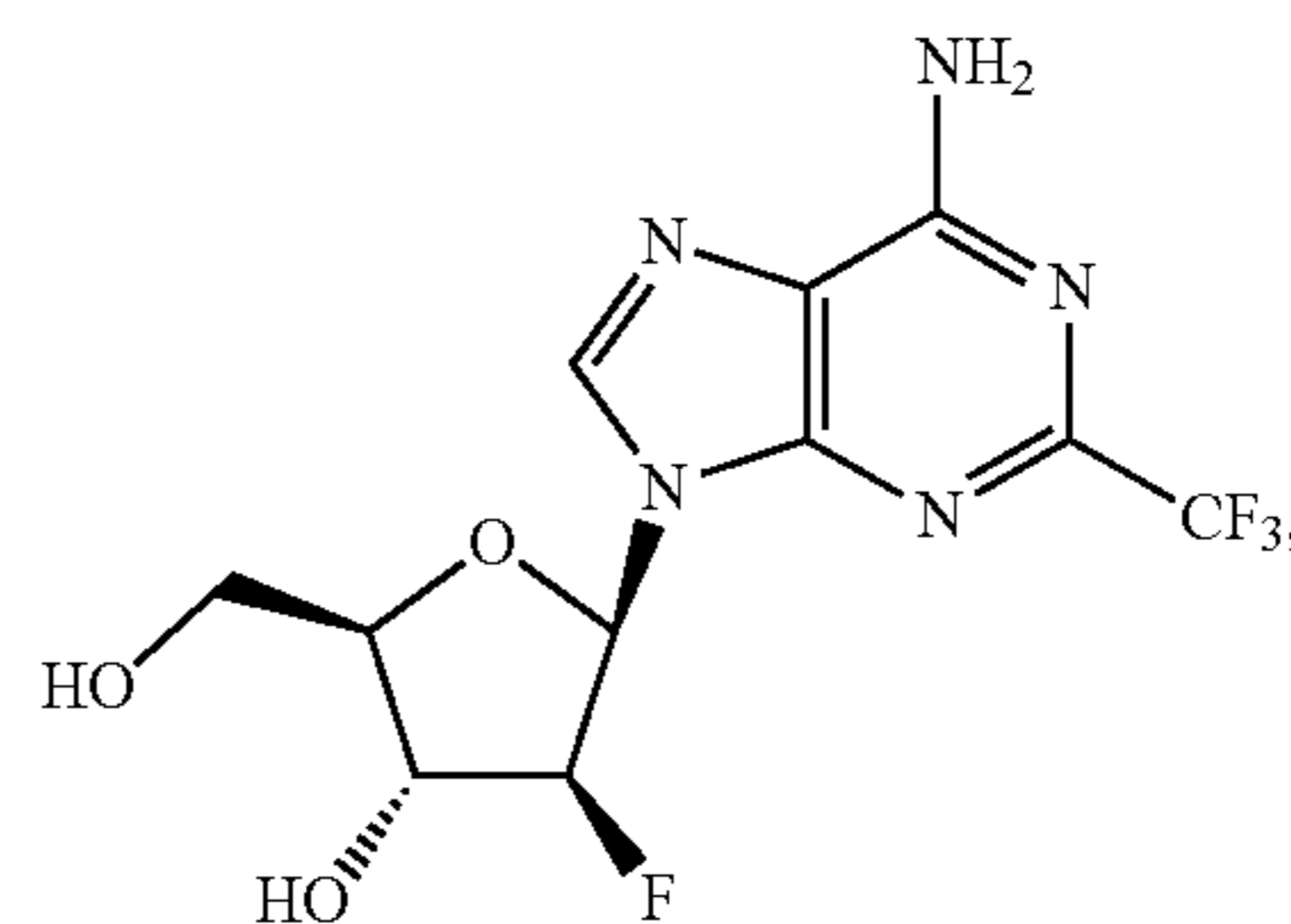
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$-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



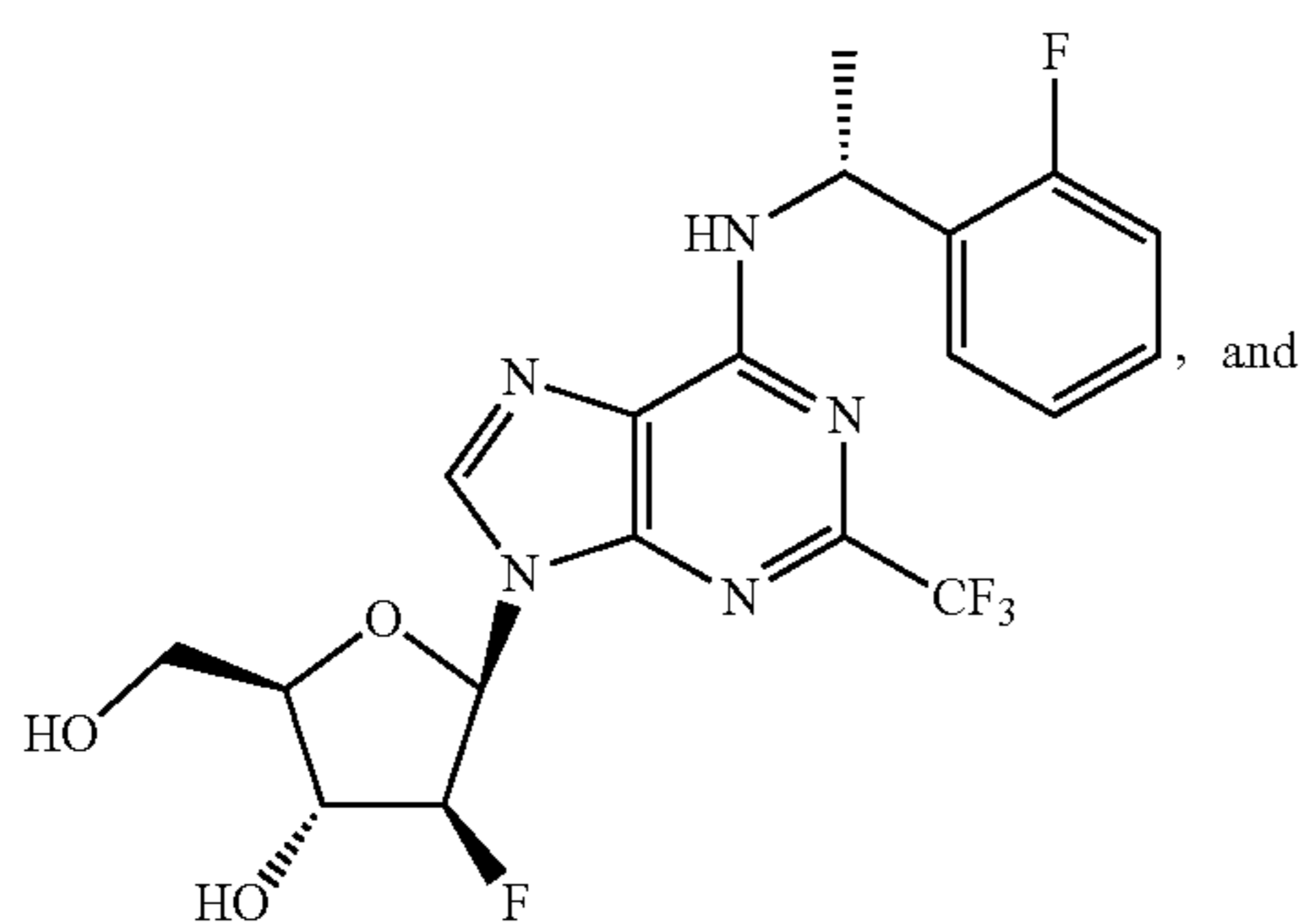
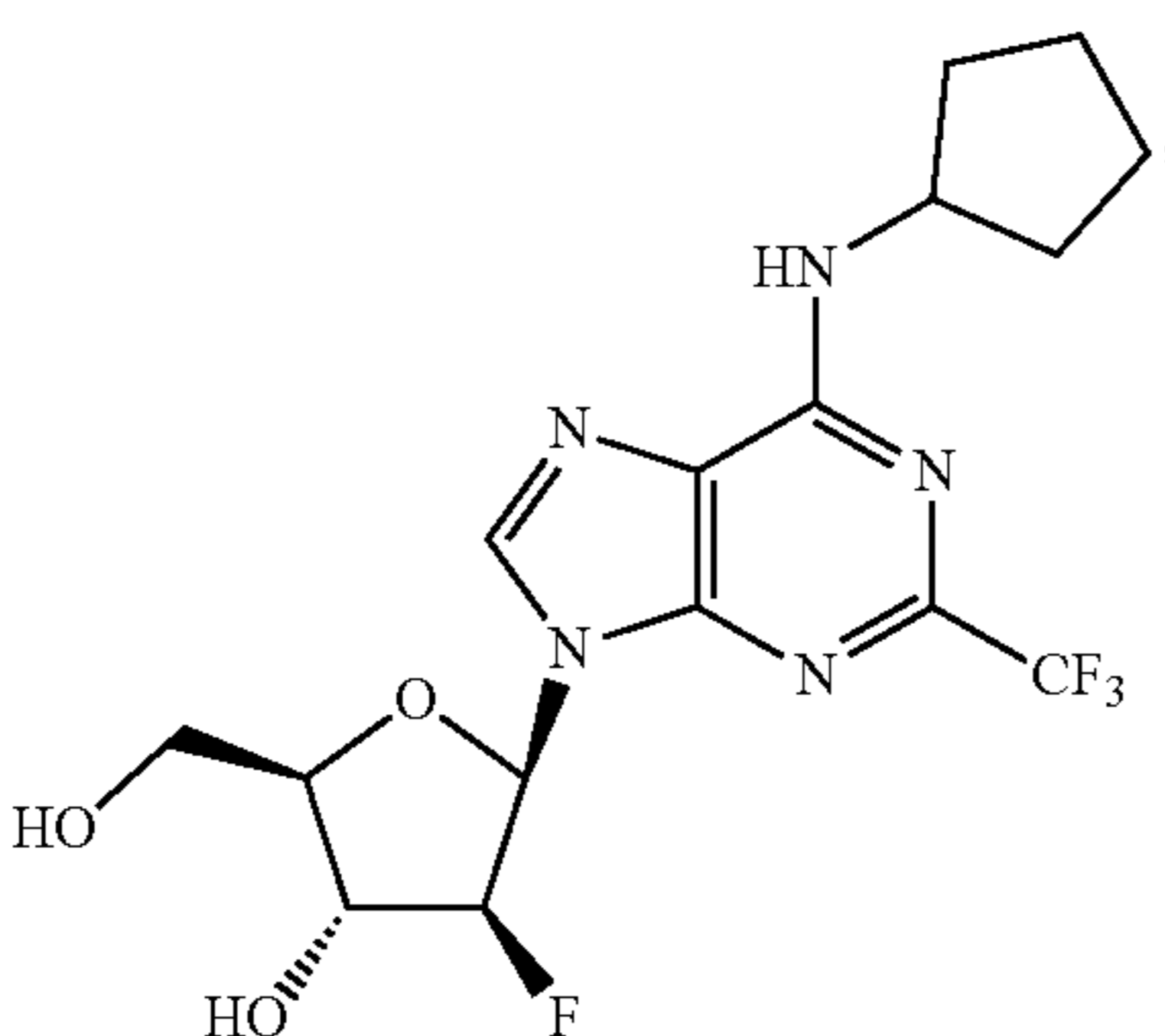
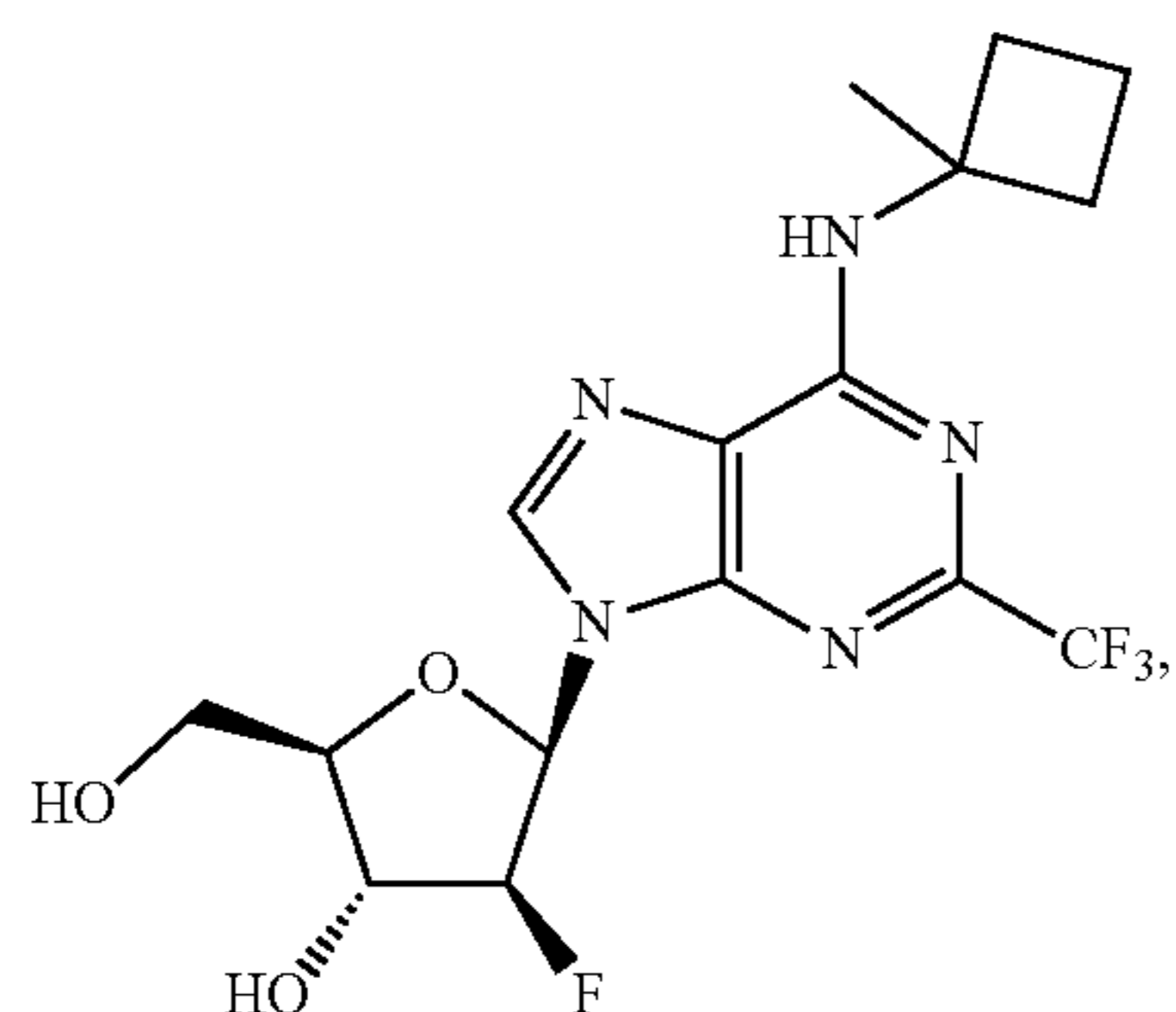
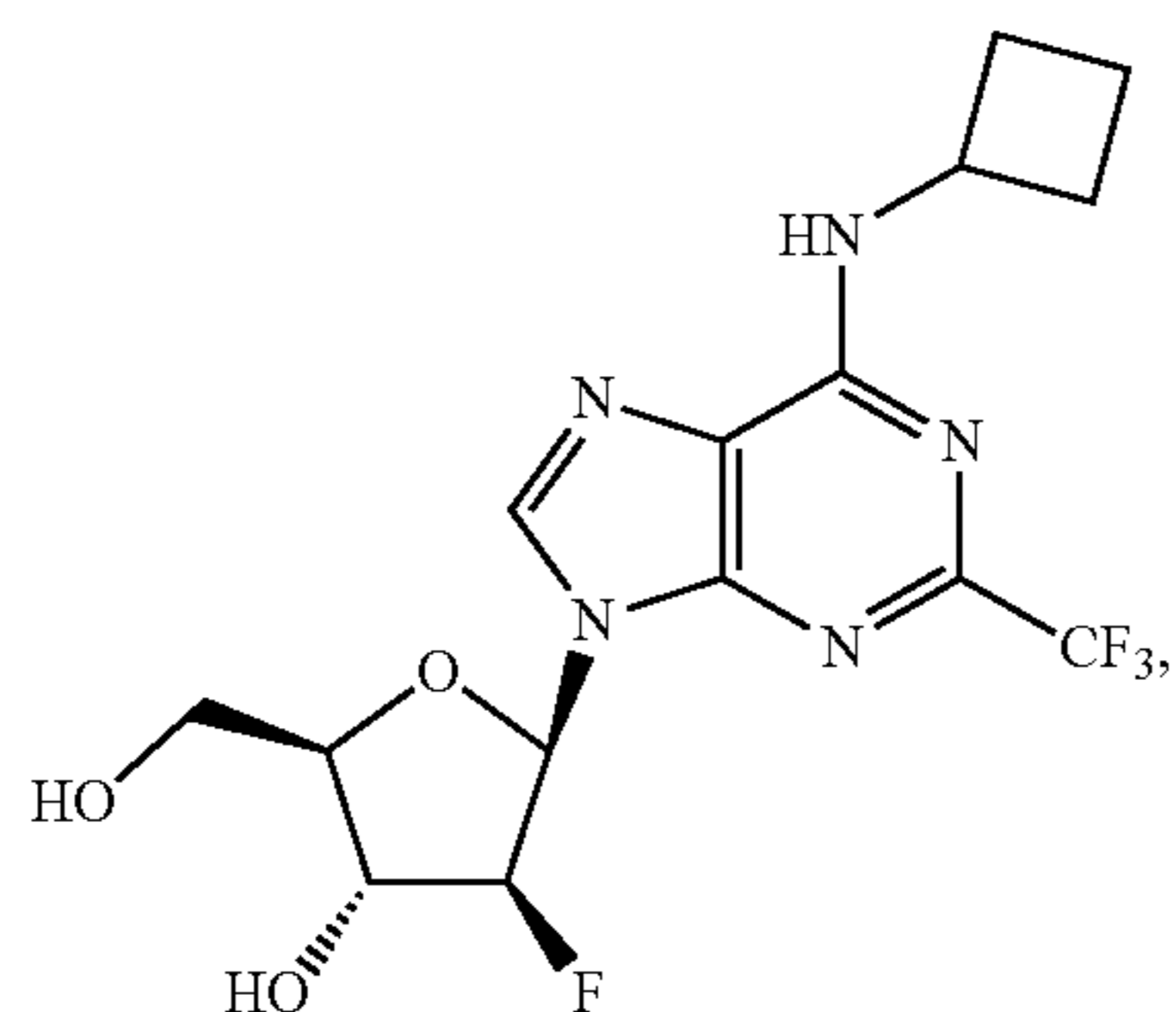
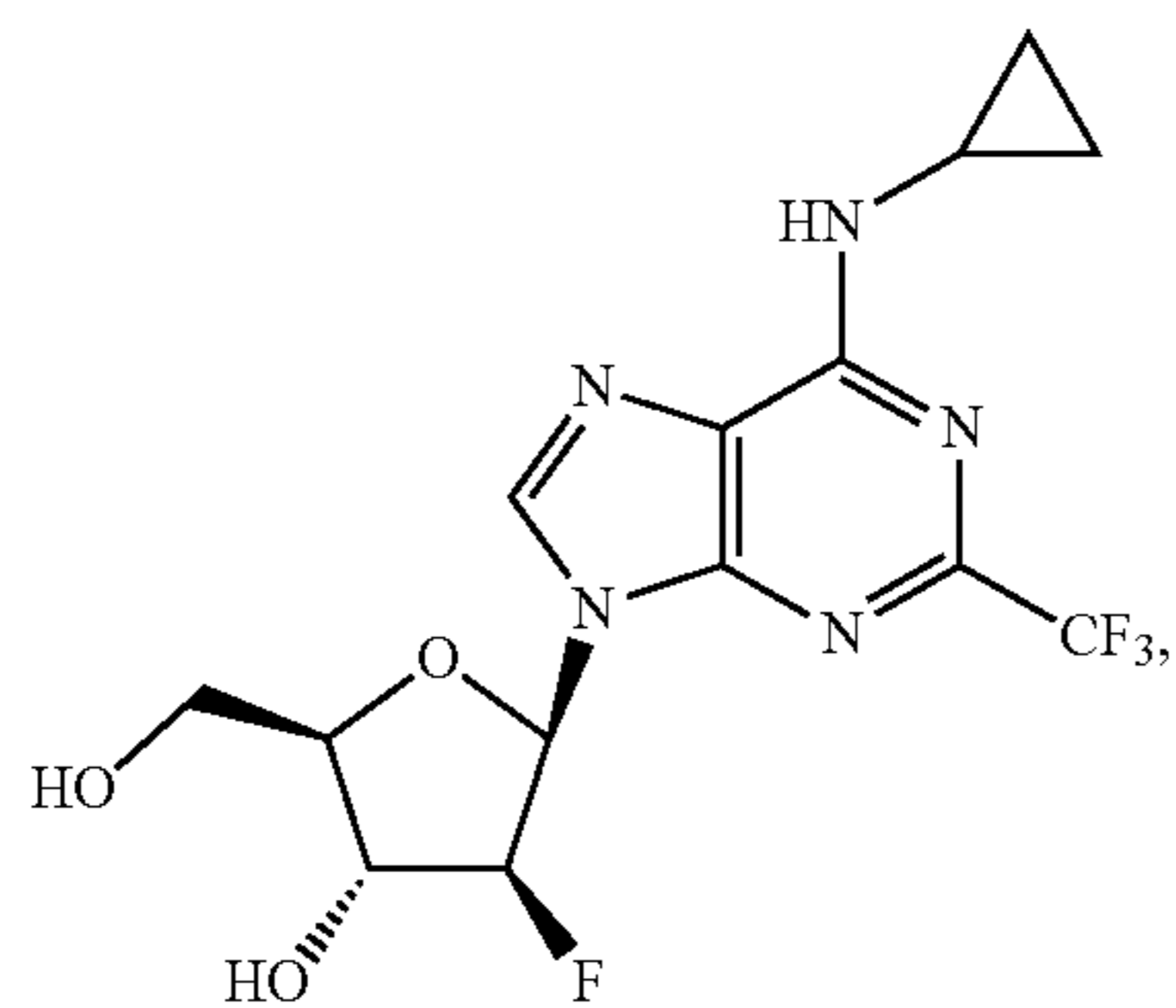
wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-\text{OH}$, C1-C12 alkyl, C1-C12 alkoxy, $-C(O)R^{14}$, $-(\text{C1-C12 alkyl})\text{CO}_2\text{H}$, and $-(\text{C1-C6 alkyl})\text{Cy}^2$; wherein R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)R^{20}$; wherein R^{21} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8 alkyl})\text{CO}_2\text{H}$, $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^3 , and $-(\text{C1-C8 alkyl})\text{Cy}^3$; wherein Cy^3 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy^2 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine, provided that when each of R^1 , R^2 , R^{3a} , and R^{3b} are not simultaneously hydrogen, and provided that when each of R^1 , R^2 , and R^{3a} is hydrogen then R^{3b} is not $-\text{CH}_2(\text{unsubstituted cyclohexyl})$, or a pharmaceutically acceptable salt thereof, thereby modifying nucleic acid synthesis in the subject.

Also disclosed are methods of modifying nucleic acid synthesis in a subject, the method comprising administering to the subject an effective amount of a compound having a structure selected from:



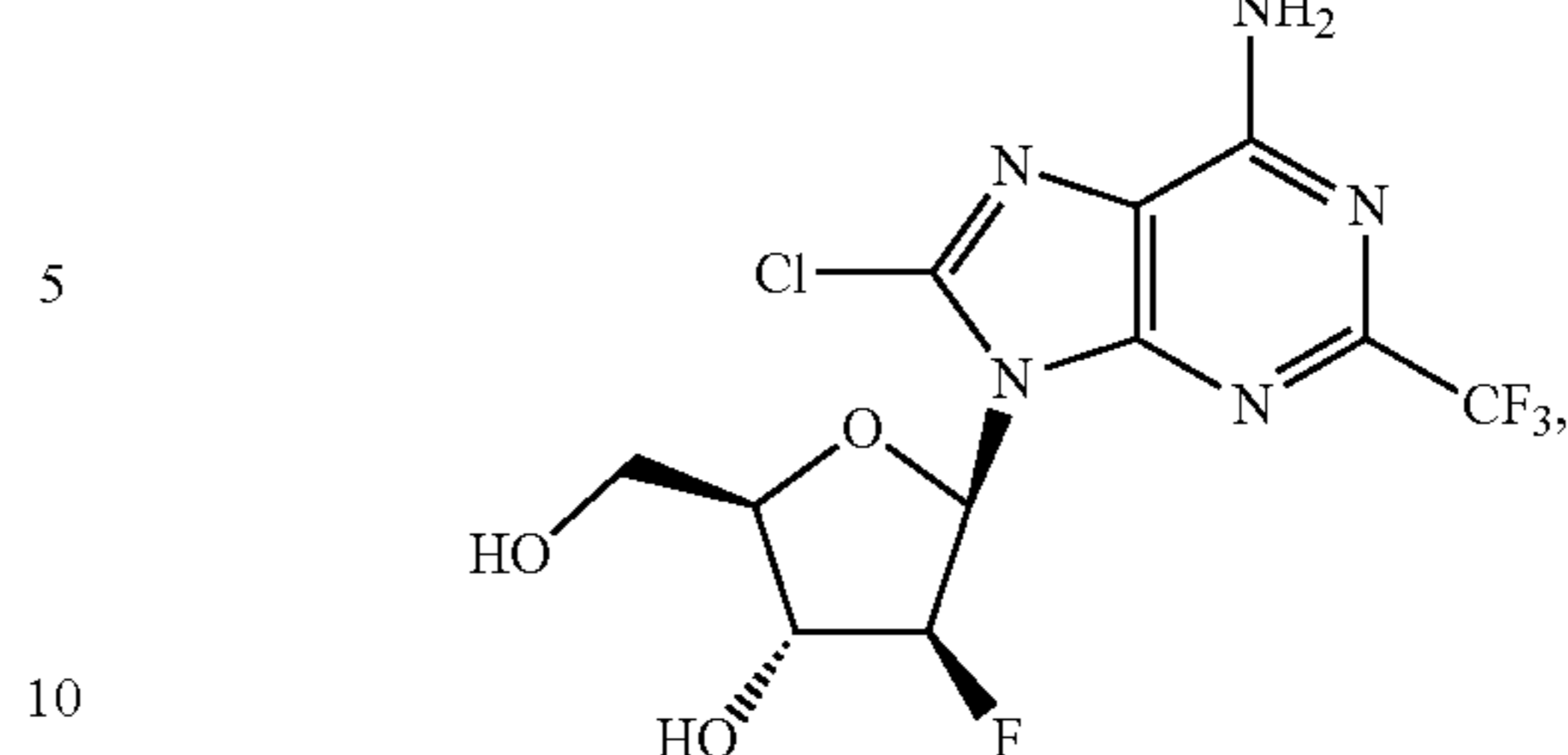
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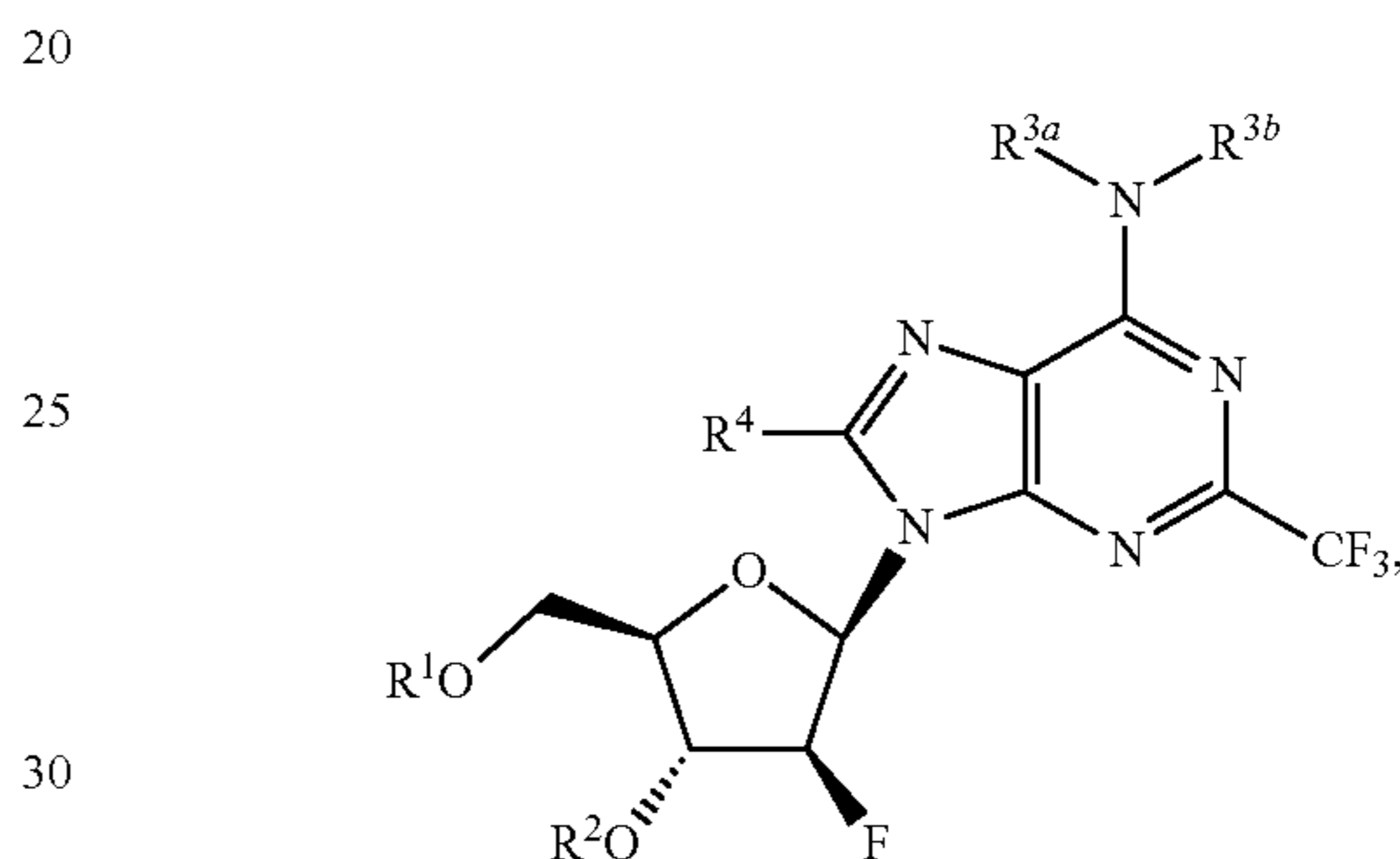
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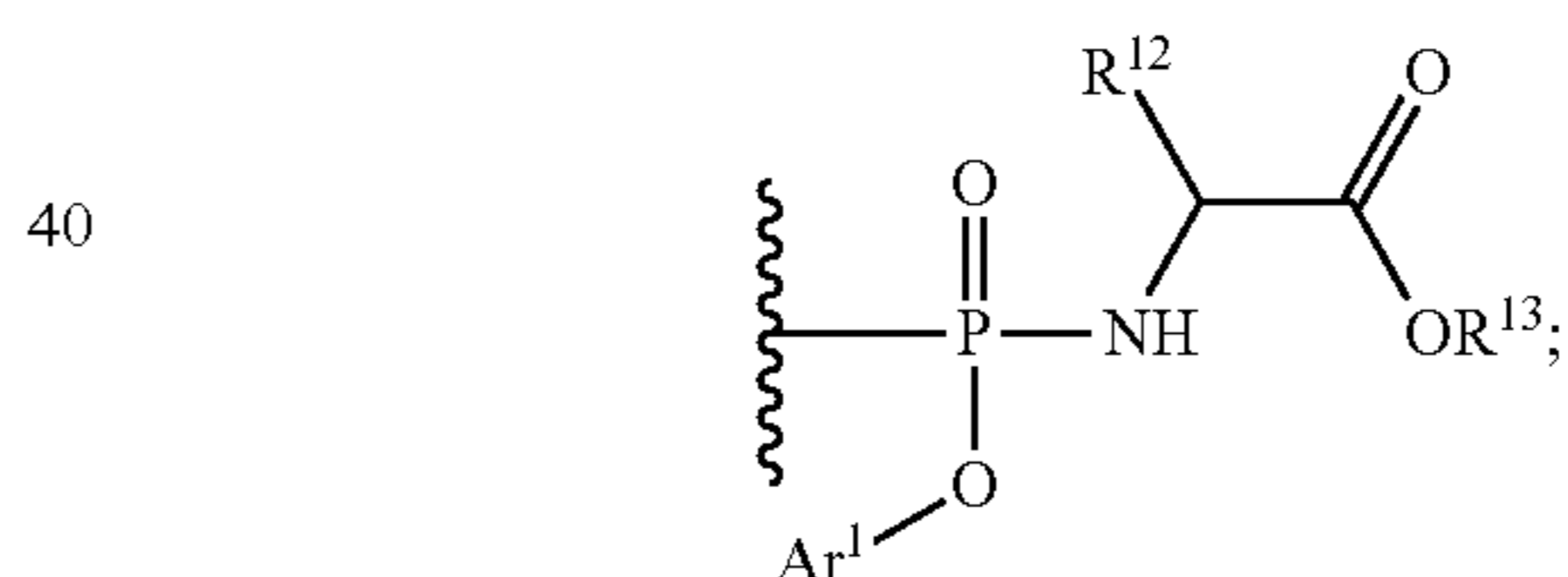


or a pharmaceutically acceptable salt thereof, thereby modifying nucleic acid synthesis in the subject.

Also disclosed are methods of modifying nucleic acid synthesis in a cell, the method comprising contacting the cell with an effective amount of a compound having a structure represented by a formula:



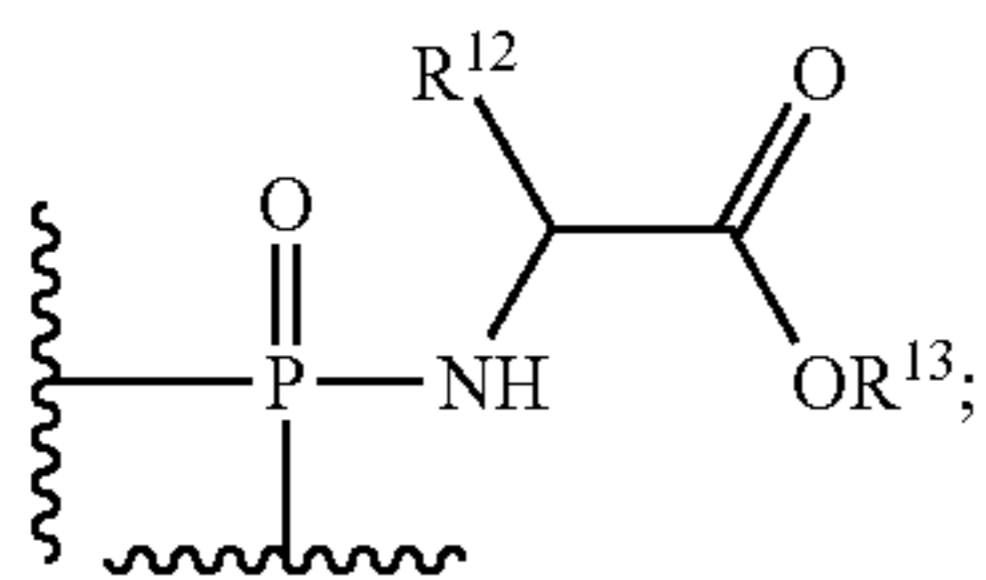
wherein one of R¹ and R² is hydrogen, and the other is selected from hydrogen, —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:



wherein R¹⁰, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH₂)R²⁰; wherein R²⁰, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, —(C1-C8 alkyl)NHC(NH)NH₂, —(C1-C8 alkyl)CO₂H, —(C1-C8 alkyl)C(O)NH₂, Cy¹, and —(C1-C8 alkyl)Cy¹; wherein Cy¹, when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R¹¹, when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, —(C1-C10 alkyl)CO₂(C1-C10 alkyl), —(C1-C10 alkyl)CO₂(C1-C10 alkylthiol), —(C1-C10 alkyl)-S-S-(C1-C10 alkyl), and Ar²; wherein Ar², when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl,

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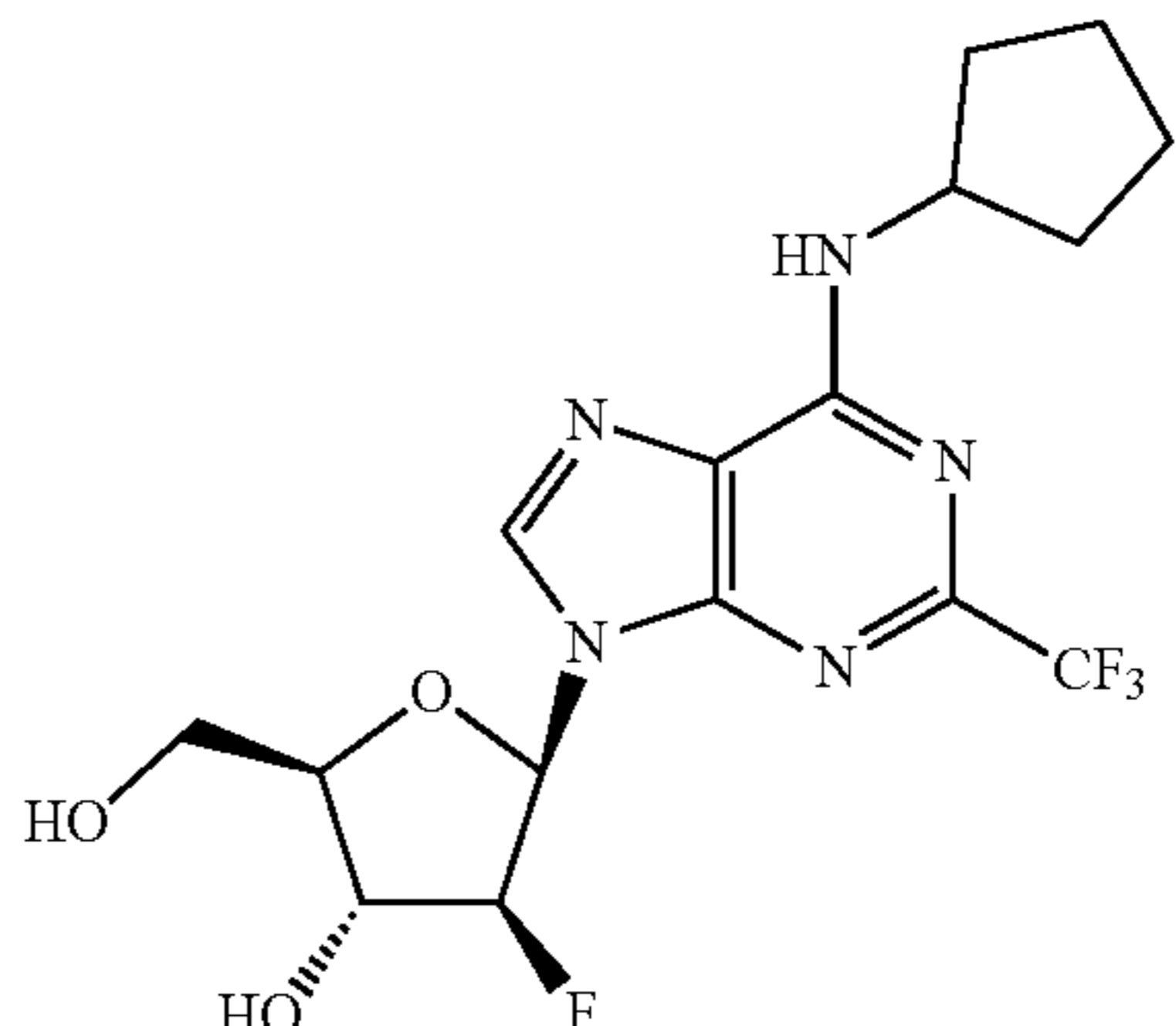
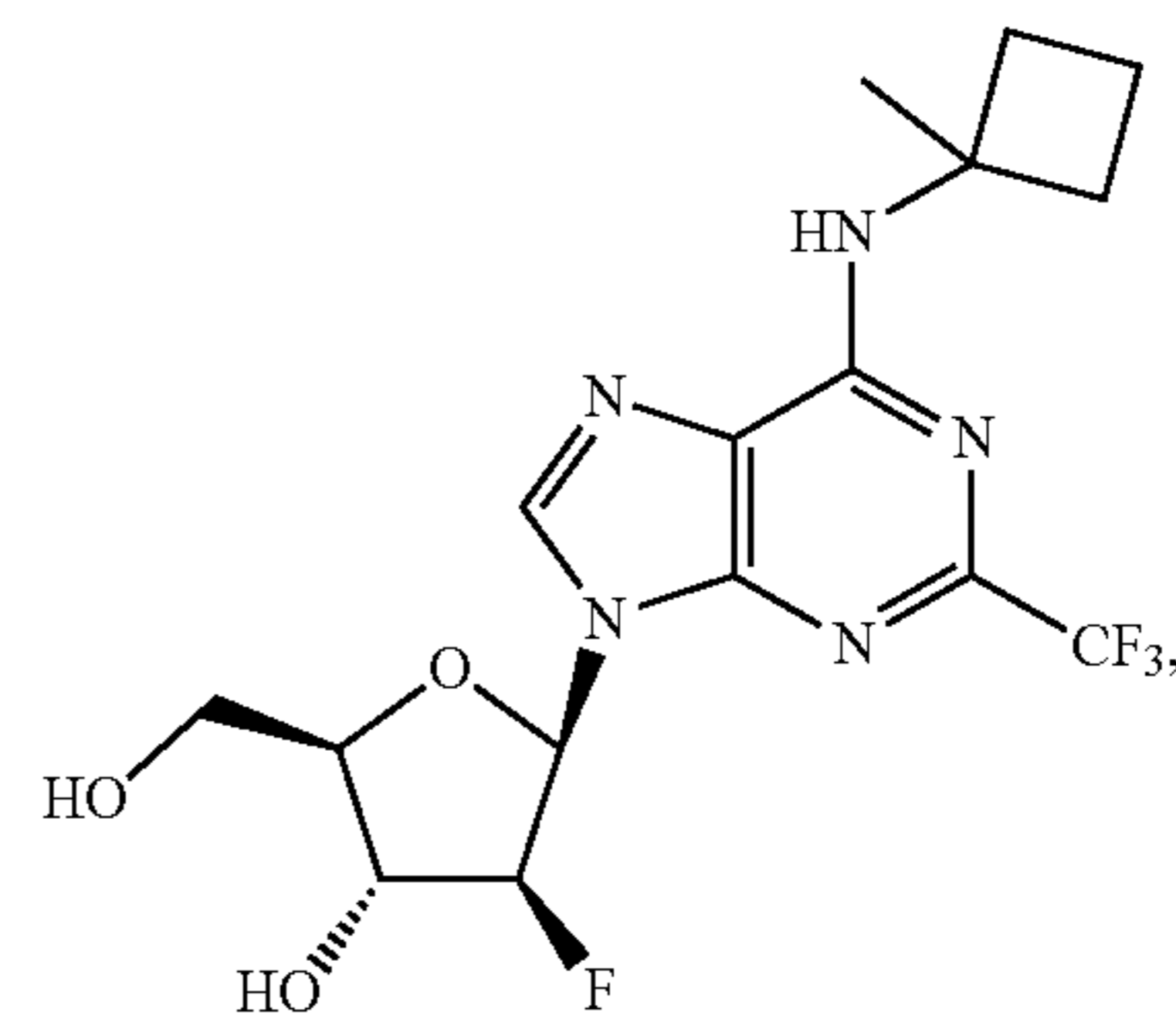
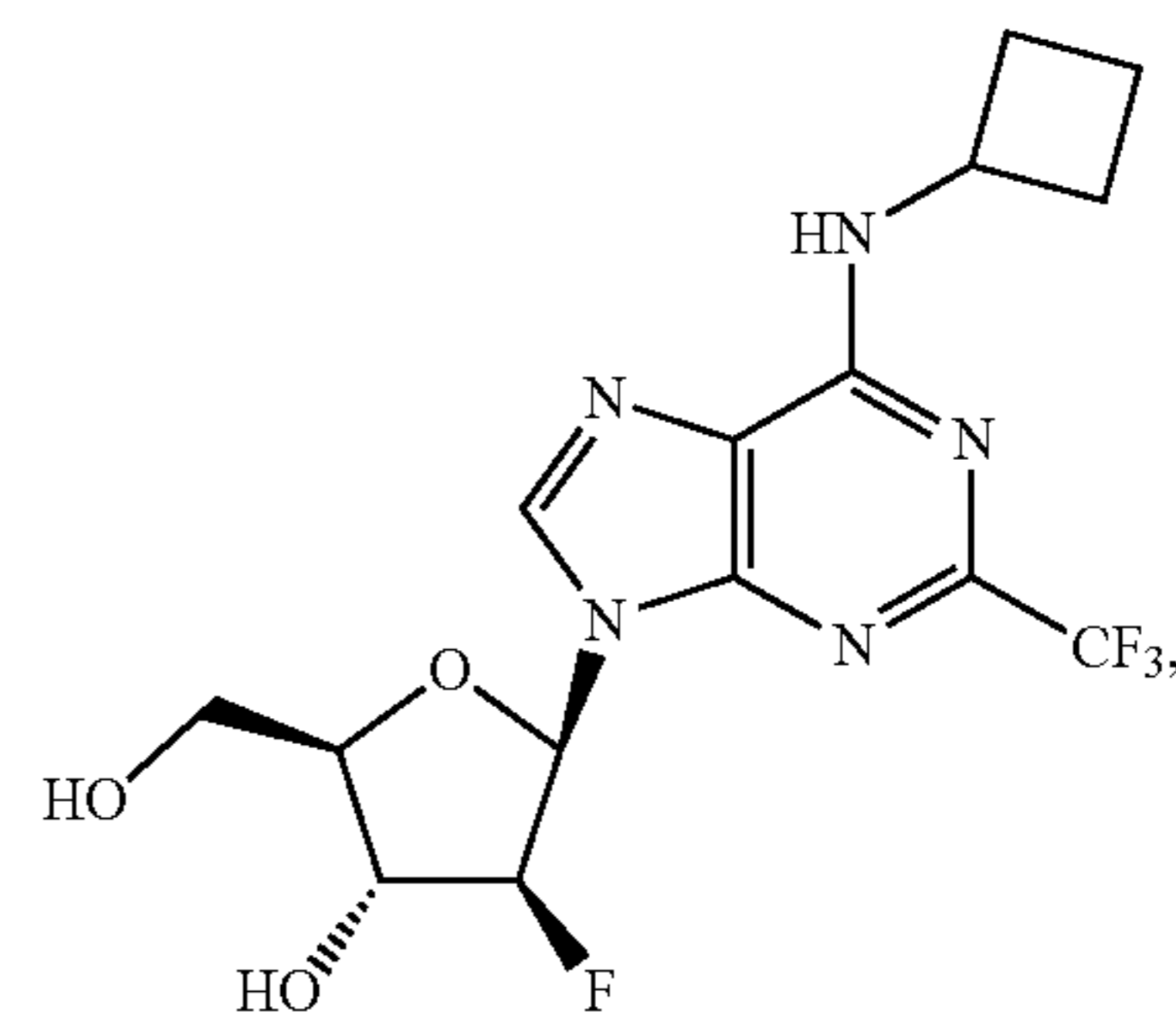
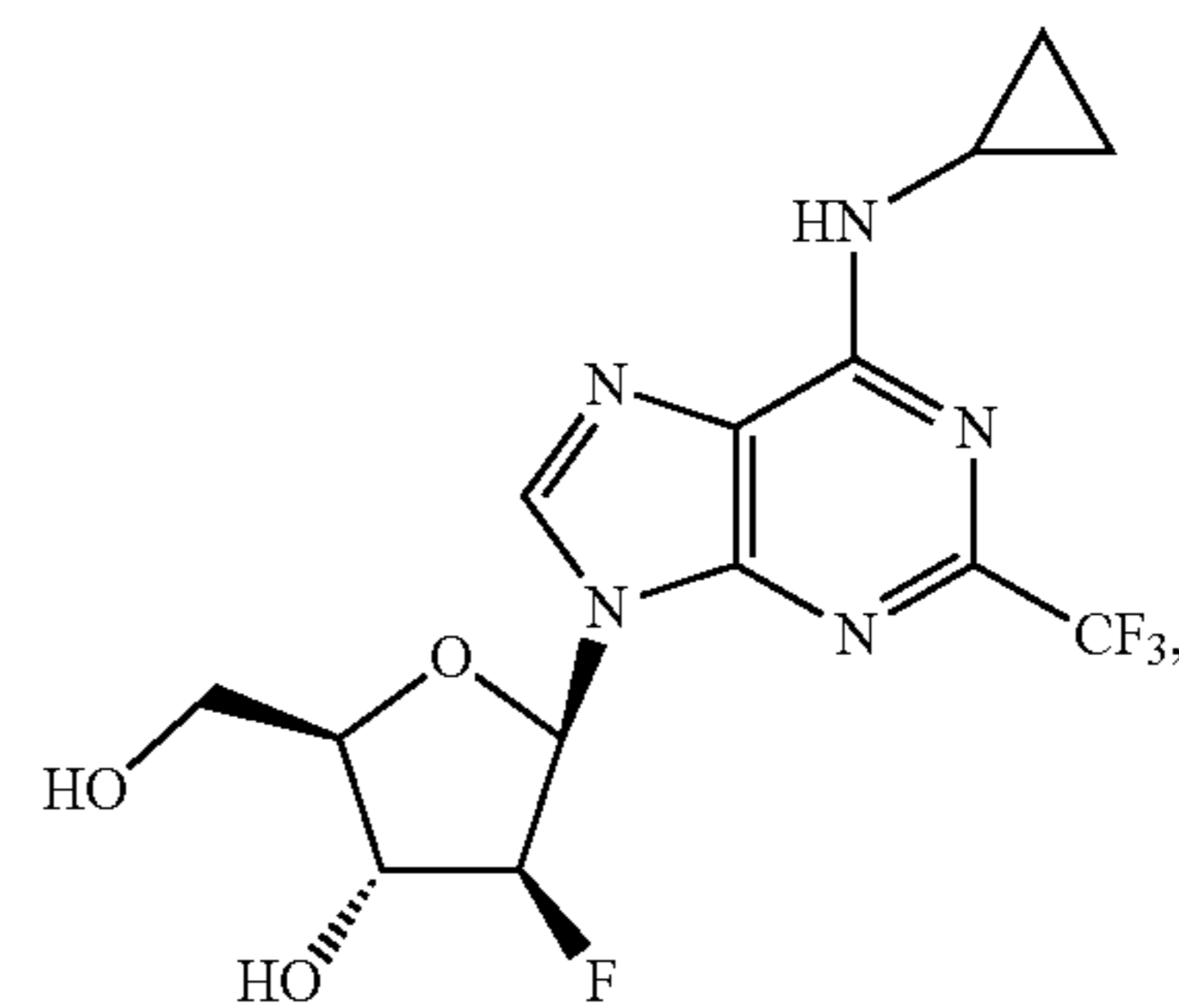
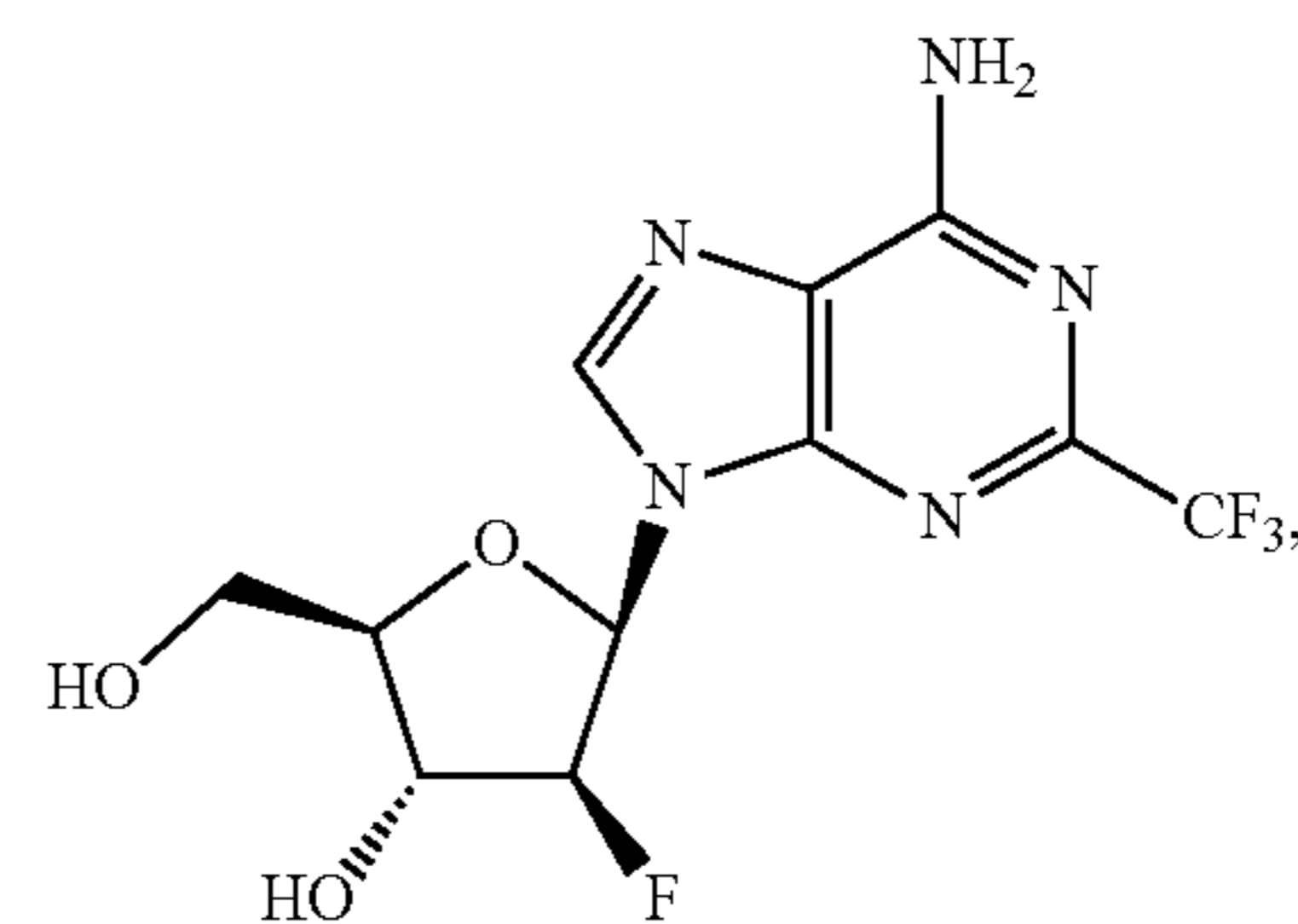
C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



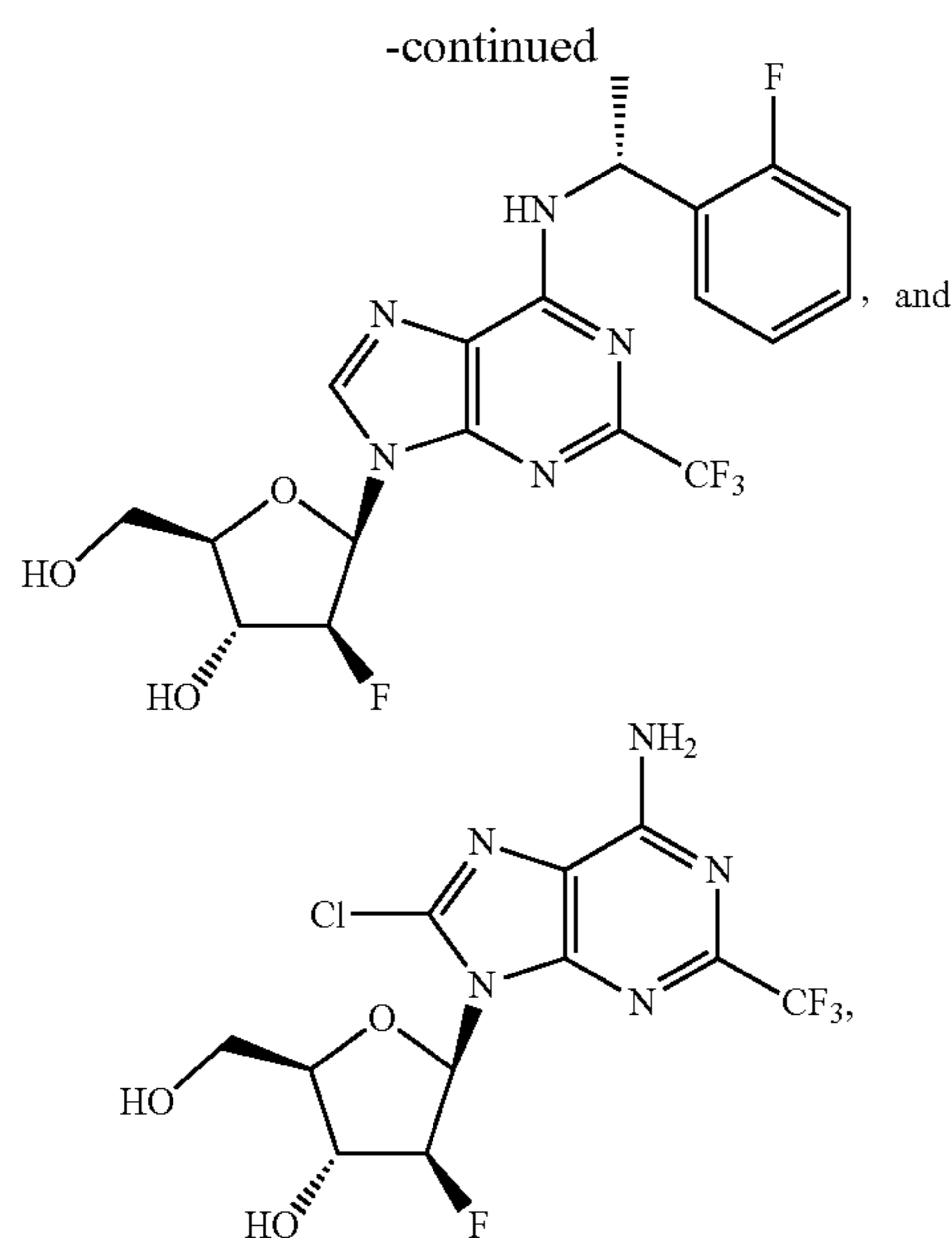
wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-OH$, C1-C12 alkyl, C1-C12 alkoxy, $-C(O)R^{14}$, $-(C1-C12\text{ alkyl})CO_2H$, and $-(C1-C6\text{ alkyl})Cy^2$; wherein R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{21}$; wherein R^{21} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(C1-C8\text{ alkyl})NHC(NH)NH_2$, $-(C1-C8\text{ alkyl})CO_2H$, $-(C1-C8\text{ alkyl})C(O)NH_2$, Cy^3 , and $-(C1-C8\text{ alkyl})Cy^3$; wherein Cy^3 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy^2 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine, provided that when each of R^1 , R^2 , R^{3a} , and R^{3b} are not simultaneously hydrogen, and provided that when each of R^1 , R^2 , and R^{3a} is hydrogen then R^{3b} is not $-CH_2$ (unsubstituted cyclohexyl), or a pharmaceutically acceptable salt thereof, thereby modifying nucleic acid synthesis in the cell.

Also disclosed are methods of modifying nucleic acid synthesis in a cell, the method comprising contacting the cell with an effective amount of a compound having a structure selected from:

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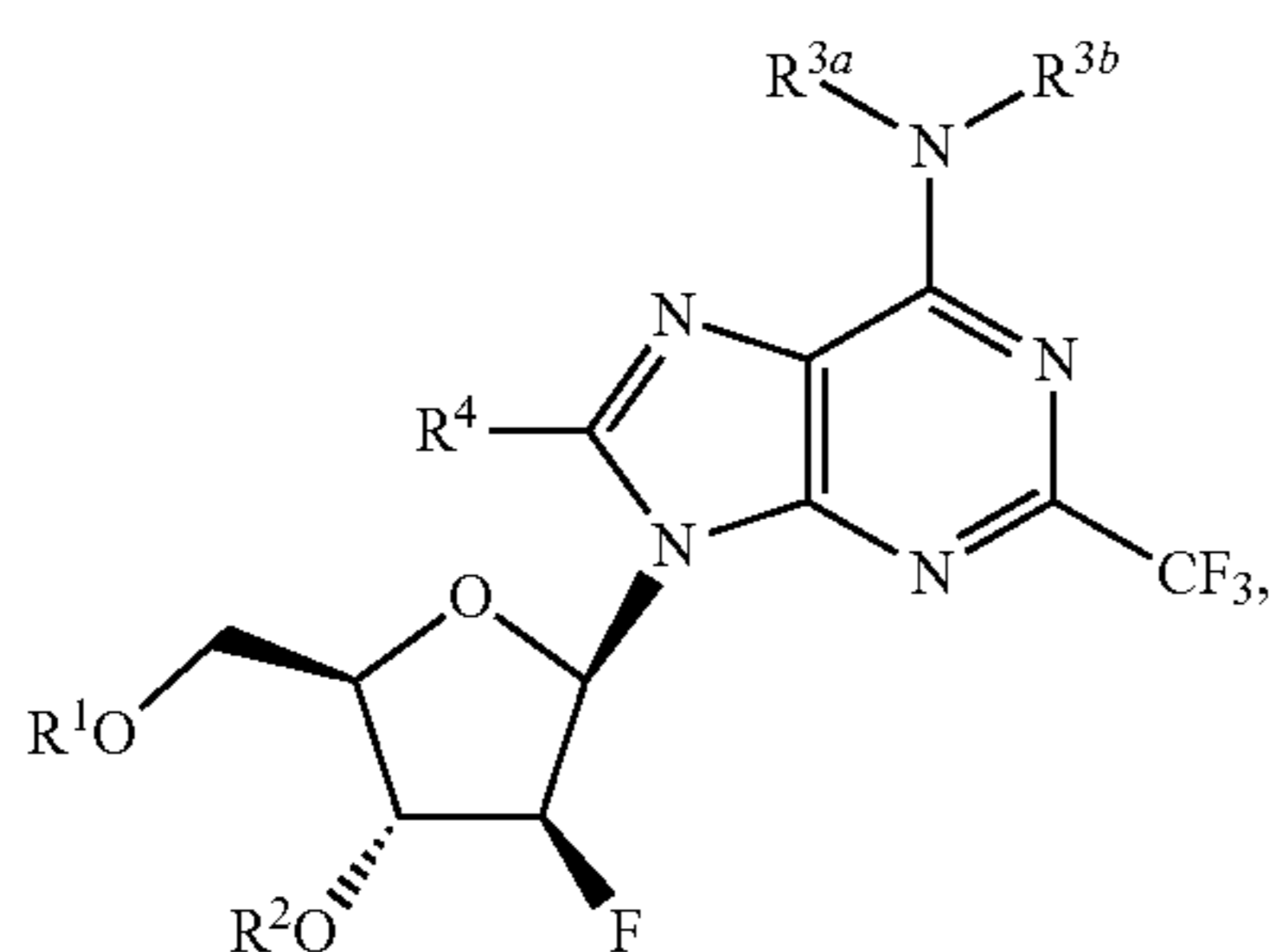


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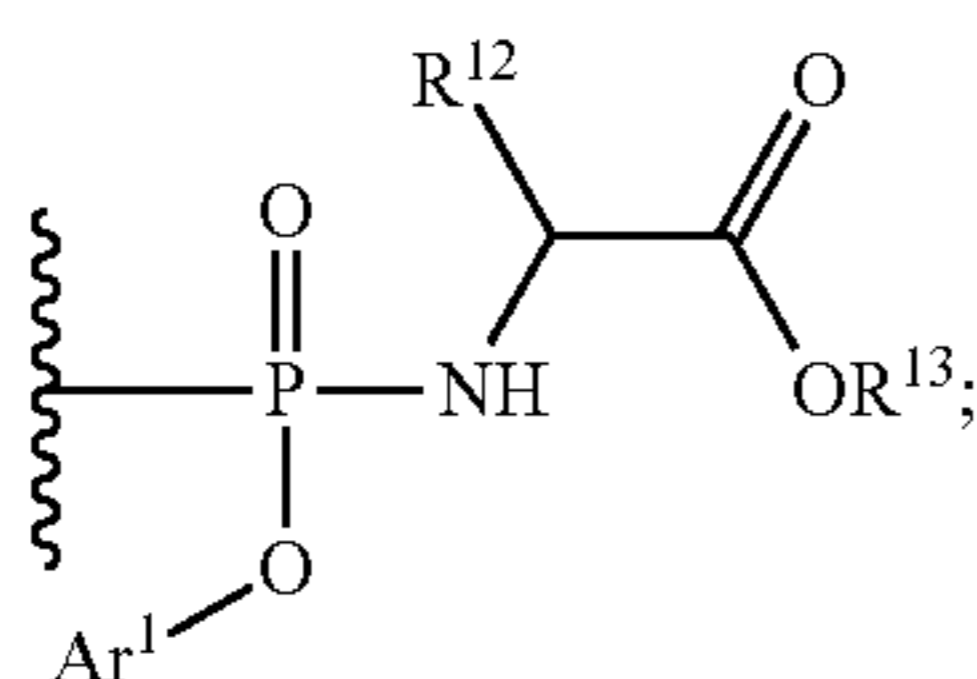


or a pharmaceutically acceptable salt thereof, thereby modifying nucleic acid synthesis in the cell.

Also disclosed are kits comprising a compound having a structure represented by a formula:



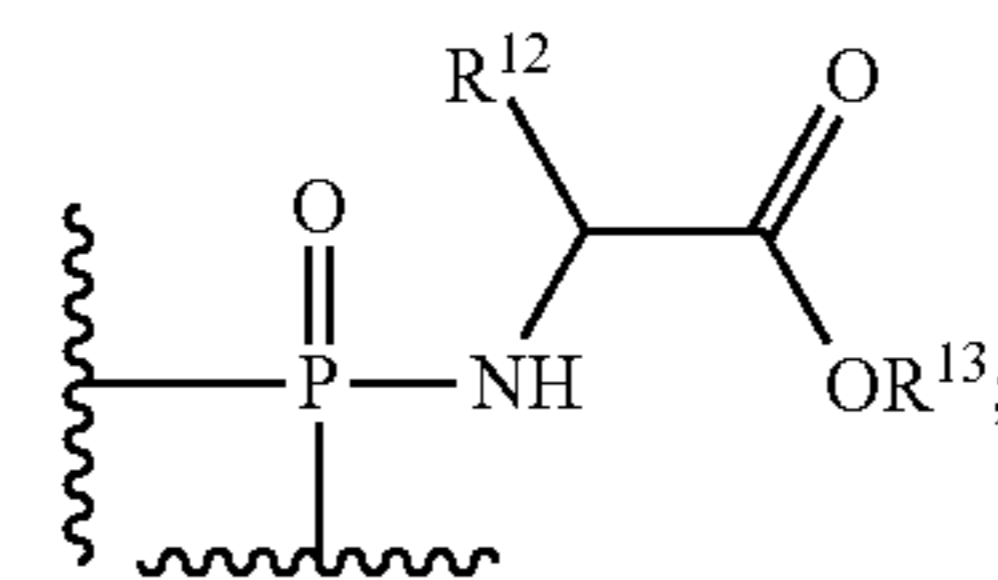
wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:



wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(C1-C8 \text{ alkyl})NHC(NH)NH_2$, $-(C1-C8 \text{ alkyl})CO_2H$, $-(C1-C8 \text{ alkyl})C(O)NH_2$, Cy^1 , and $-(C1-C8 \text{ alkyl})Cy^1$; wherein Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4

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haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $-(C1-C10 \text{ alkyl})CO_2(C1-C10 \text{ alkyl})$, $-(C1-C10 \text{ alkyl})CO_2(C1-C10 \text{ alkylthiol})$, $-(C1-C10 \text{ alkyl})-S-S-(C1-C10 \text{ alkyl})$, and Ar^2 ; wherein Ar^2 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:

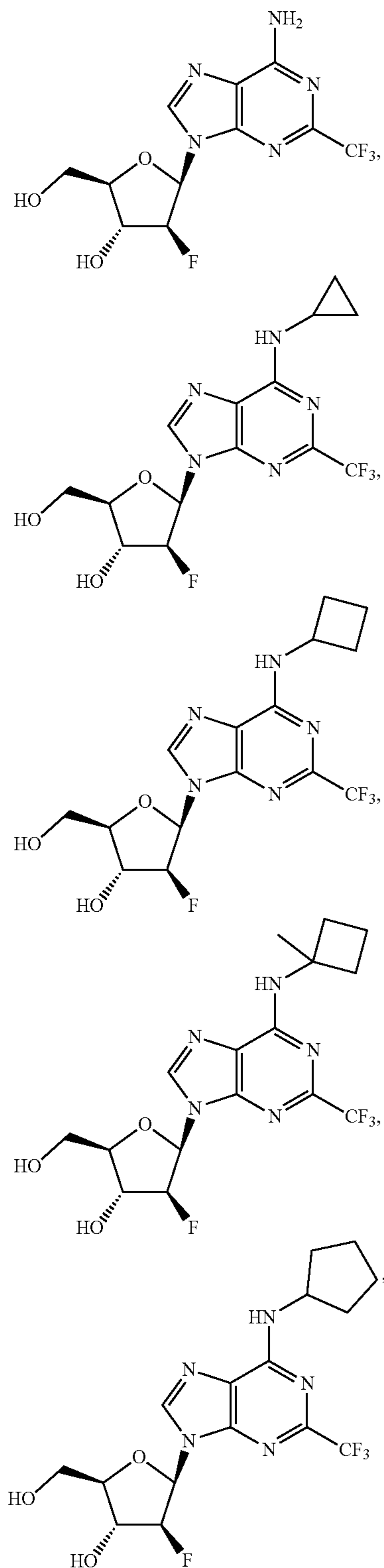


wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-OH$, C1-C12 alkyl, C1-C12 alkoxy, $-C(O)R^{14}$, $-(C1-C12 \text{ alkyl})CO_2H$, and $-(C1-C6 \text{ alkyl})Cy^2$; wherein R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{21}$; wherein R^{21} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(C1-C8 \text{ alkyl})NHC(NH)NH_2$, $-(C1-C8 \text{ alkyl})CO_2H$, $-(C1-C8 \text{ alkyl})C(O)NH_2$, Cy^3 , and $-(C1-C8 \text{ alkyl})Cy^3$; wherein Cy^3 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy^2 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine, provided that when each of R^1 , R^2 , R^{3a} , and R^{3b} are not simultaneously hydrogen, and provided that when each of R^1 , R^2 , and R^{3a} is hydrogen then R^{3b} is not

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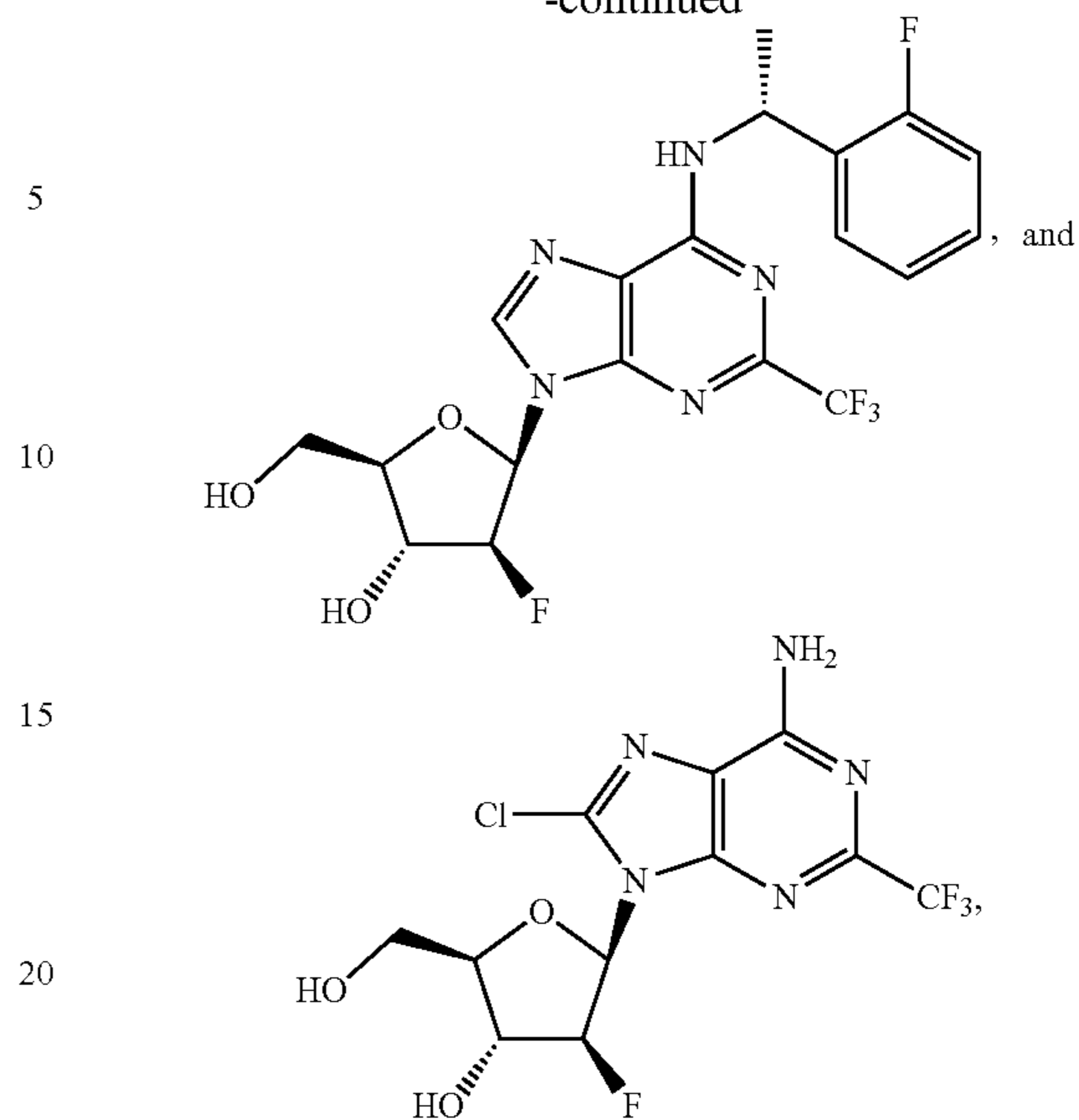
—CH₂(unsubstituted cyclohexyl), or a pharmaceutically acceptable salt thereof, and one or more of: (a) a chemotherapeutic agent; (b) instructions for administering the compound in connection with treating cancer; and (c) instructions for treating cancer.

Also disclosed are kits comprising a compound having a structure selected from:



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or a pharmaceutically acceptable salt thereof, and one or more of: (a) a chemotherapeutic agent; (b) instructions for administering the compound in connection with treating cancer; and (c) instructions for treating cancer.

While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

BRIEF DESCRIPTION OF THE FIGURES

The above and other objects, features and advantages of the present invention will become more apparent to those of ordinary skill in the art by describing in detail exemplary embodiments thereof with reference to the accompanying drawings.

FIG. 1 shows representative data illustrating that administration of 25 mg/kg compound no. 5 effectively reduces tumor volume in a solid tumor, triple negative breast cancer mice model.

FIG. 2 shows representative data illustrating the results of a basic dose escalation test for tolerance of drug concentration.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is

to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION

The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein may be different from the actual publication dates, which can require independent confirmation.

A. Definitions

As used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a functional group,” “an alkyl,” or “a residue” includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

As used in the specification and in the claims, the term “comprising” can include the aspects “consisting of” and “consisting essentially of.”

Ranges can be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another aspect includes

from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

As used herein, the terms “about” and “at or about” mean that the amount or value in question can be the value designated some other value approximately or about the same. It is generally understood, as used herein, that it is the nominal value indicated $\pm 10\%$ variation unless otherwise indicated or inferred. The term is intended to convey that similar values promote equivalent results or effects recited in the claims. That is, it is understood that amounts, sizes, formulations, parameters, and other quantities and characteristics are not and need not be exact, but can be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art. In general, an amount, size, formulation, parameter or other quantity or characteristic is “about” or “approximate” whether or not expressly stated to be such. It is understood that where “about” is used before a quantitative value, the parameter also includes the specific quantitative value itself, unless specifically stated otherwise.

References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

As used herein, “ IC_{50} ” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an IC_{50} can refer to the concentration of a substance that is required for 50% inhibition in vivo, as further defined elsewhere herein. In a further aspect, IC_{50} refers to the half-maximal (50%) inhibitory concentration (IC) of a substance.

As used herein, “ EC_{50} ” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% agonism of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an EC_{50} can refer to the concentration of a substance that is required for 50% agonism in vivo, as further defined elsewhere herein. In a further aspect, EC_{50} refers to the concentration of agonist that provokes a response halfway between the baseline and maximum response.

As used herein, the terms “optional” or “optionally” means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

As used herein, the term “subject” can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term “patient” includes human and veterinary subjects.

As used herein, the term “treatment” refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term “subject” also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.).

As used herein, the term “prevent” or “preventing” refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

As used herein, the term “diagnosed” means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein.

As used herein, the terms “administering” and “administration” refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable

such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

As used herein, the terms “effective amount” and “amount effective” refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a “therapeutically effective amount” refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a “prophylactically effective amount”; that is, an amount effective for prevention of a disease or condition.

As used herein, “dosage form” means a pharmacologically active material in a medium, carrier, vehicle, or device suitable for administration to a subject. A dosage forms can comprise inventive a disclosed compound, a product of a disclosed method of making, or a salt, solvate, or polymorph thereof, in combination with a pharmaceutically acceptable excipient, such as a preservative, buffer, saline, or phosphate buffered saline. Dosage forms can be made using conventional pharmaceutical manufacturing and compounding techniques. Dosage forms can comprise inorganic or organic buffers (e.g., sodium or potassium salts of phosphate, carbonate, acetate, or citrate) and pH adjustment agents (e.g., hydrochloric acid, sodium or potassium hydroxide, salts of citrate or acetate, amino acids and their salts) antioxidants (e.g., ascorbic acid, alpha-tocopherol), surfactants (e.g., polysorbate 20, polysorbate 80, polyoxyethylene9-10 nonyl phenol, sodium desoxycholate), solution and/or cryo/lyo stabilizers (e.g., sucrose, lactose, mannitol, trehalose), osmotic adjustment agents (e.g., salts or sugars), antibacterial agents (e.g., benzoic acid, phenol, gentamicin), anti-foaming agents (e.g., polydimethylsiloxane), preservatives (e.g., thimerosal, 2-phenoxyethanol, EDTA), polymeric stabilizers and viscosity-adjustment agents (e.g., polyvinylpyrrolidone, poloxamer 488, carboxymethylcellulose) and cosolvents (e.g., glycerol, polyethylene glycol, ethanol). A dosage form formulated for injectable use can have a

disclosed compound, a product of a disclosed method of making, or a salt, solvate, or polymorph thereof, suspended in sterile saline solution for injection together with a preservative.

As used herein, "kit" means a collection of at least two components constituting the kit. Together, the components constitute a functional unit for a given purpose. Individual member components may be physically packaged together or separately. For example, a kit comprising an instruction for using the kit may or may not physically include the instruction with other individual member components. Instead, the instruction can be supplied as a separate member component, either in a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation.

As used herein, "instruction(s)" means documents describing relevant materials or methodologies pertaining to a kit. These materials may include any combination of the following: background information, list of components and their availability information (purchase information, etc.), brief or detailed protocols for using the kit, trouble-shooting, references, technical support, and any other related documents. Instructions can be supplied with the kit or as a separate member component, either as a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation. Instructions can comprise one or multiple documents, and are meant to include future updates.

As used herein, the terms "therapeutic agent" include any synthetic or naturally occurring biologically active compound or composition of matter which, when administered to an organism (human or nonhuman animal), induces a desired pharmacologic, immunogenic, and/or physiologic effect by local and/or systemic action. The term therefore encompasses those compounds or chemicals traditionally regarded as drugs, vaccines, and biopharmaceuticals including molecules such as proteins, peptides, hormones, nucleic acids, gene constructs and the like. Examples of therapeutic agents are described in well-known literature references such as the Merck Index (14th edition), the Physicians' Desk Reference (64th edition), and The Pharmacological Basis of Therapeutics (12th edition), and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances that affect the structure or function of the body, or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment. For example, the term "therapeutic agent" includes compounds or compositions for use in all of the major therapeutic areas including, but not limited to, adjuvants; anti-infectives such as antibiotics and antiviral agents; anti-cancer and anti-neoplastic agents such as kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors and other DNA damage response modifiers, epigenetic agents such as bromodomain and extra-terminal (BET) inhibitors, histone deacetylase (HDAC) inhibitors, iron chelators and other ribonucleotides reductase inhibitors, proteasome inhibitors and Nedd8-activating enzyme (NAE) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, traditional cytotoxic agents such as paclitaxel, dox, irinotecan, and platinum compounds, immune checkpoint blockade agents such as cytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody (mAB), programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) mAB, cluster of

differentiation 47 (CD47) mAB, toll-like receptor (TLR) agonists and other immune modifiers, cell therapeutics such as chimeric antigen receptor T-cell (CAR-T)/chimeric antigen receptor natural killer (CAR-NK) cells, and proteins such as interferons (IFNs), interleukins (ILs), and mAbs; anti-ALS agents such as entry inhibitors, fusion inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors, NCP7 inhibitors, protease inhibitors, and integrase inhibitors; analgesics and analgesic combinations, anorexics, anti-inflammatory agents, anti-epileptics, local and general anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergics, antiarrhythmics, antihypertensive agents, hormones, and nutrients, anti-arthritics, antiasthmatic agents, anticonvulsants, antihistamines, anti-nauseants, antineoplastics, antipruritics, antipyretics; antispasmodics, cardiovascular preparations (including calcium channel blockers, beta-blockers, beta-agonists and antiarrhythmics), antihypertensives, diuretics, vasodilators; central nervous system stimulants; cough and cold preparations; decongestants; diagnostics; hormones; bone growth stimulants and bone resorption inhibitors; immunosuppressives; muscle relaxants; psychostimulants; sedatives; tranquilizers; proteins, peptides, and fragments thereof (whether naturally occurring, chemically synthesized or recombinantly produced); and nucleic acid molecules (polymeric forms of two or more nucleotides, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) including both double- and single-stranded molecules, gene constructs, expression vectors, antisense molecules and the like), small molecules (e.g., doxorubicin) and other biologically active macromolecules such as, for example, proteins and enzymes. The agent may be a biologically active agent used in medical, including veterinary, applications and in agriculture, such as with plants, as well as other areas. The term "therapeutic agent" also includes without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of disease or illness; or substances which affect the structure or function of the body; or pro-drugs, which become biologically active or more active after they have been placed in a predetermined physiological environment.

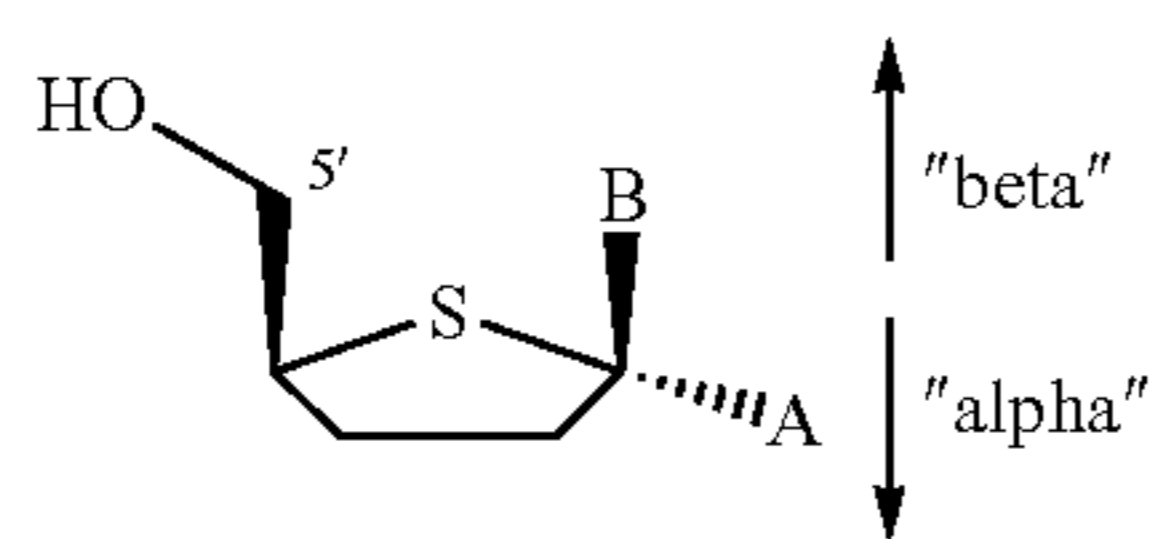
The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

As used herein, the term "derivative" refers to a compound having a structure derived from the structure of a parent compound (e.g., a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

As used herein, the term "pharmaceutically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene

glycol, polyethylene glycol and the like), carboxymethyl-cellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microcapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

As used herein, when referring to a substituent on a sugar ring of a nucleoside or nucleotide, the term "beta" means a substituent on the same side of the plane of the sugar ring as the 5' carbon and the term "alpha" means a substituent on the opposite side of the plane of the sugar ring from the 5' carbon. Thus, as shown below, substituent "A" is in the "alpha" position and substituent "B" is in the "beta" position with respect to the 5' carbon.



As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the

substituted atom and the substituent, and that the substitution results in a stable compound, e.g., a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

In defining various terms, "A¹," "A²," "A³," and "A⁴" are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

The term "aliphatic" or "aliphatic group," as used herein, denotes a hydrocarbon moiety that may be straight-chain (i.e., unbranched), branched, or cyclic (including fused, bridging, and spirofused polycyclic) and may be completely saturated or may contain one or more units of unsaturation, but which is not aromatic. Unless otherwise specified, aliphatic groups contain 1-20 carbon atoms. Aliphatic groups include, but are not limited to, linear or branched, alkyl, alkenyl, and alkynyl groups, and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, s-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can be cyclic or acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (e.g., from one to four) carbon atoms. The term alkyl group can also be a C1 alkyl, C1-C2 alkyl, C1-C3 alkyl, C1-C4 alkyl, C1-C5 alkyl, C1-C6 alkyl, C1-C7 alkyl, C1-C8 alkyl, C1-C9 alkyl, C1-C10 alkyl, and the like up to and including a C1-C24 alkyl.

Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" or "haloalkyl" specifically refers to an alkyl group that is substituted with one or more halide, e.g., fluorine, chlorine, bromine, or iodine. Alternatively, the term "monohaloalkyl" specifically refers to an alkyl group that is substituted with a single halide, e.g. fluorine, chlorine, bromine, or iodine. The term "polyhaloalkyl" specifically refers to an alkyl group that is independently substituted with two or more halides, i.e. each halide substituent need not be the same halide as another halide substituent, nor do the multiple instances of a halide substituent need to be on the same carbon. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "aminoalkyl" specifically refers to an alkyl group that is substituted with one or more amino groups. The term "hydroxyalkyl" specifically refers to an alkyl group that is substituted with one or more hydroxy groups. When "alkyl" is used in one instance and a specific term such as "hydroxyalkyl" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "hydroxyalkyl" and the like.

This practice is also used for other groups described herein. That is, while a term such as “cycloalkyl” refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, e.g., an “alkylcycloalkyl.” Similarly, a substituted alkoxy can be specifically referred to as, e.g., a “halogenated alkoxy,” a particular substituted alkenyl can be, e.g., an “alkenylalcohol,” and the like. Again, the practice of using a general term, such as “cycloalkyl,” and a specific term, such as “alkylcycloalkyl,” is not meant to imply that the general term does not also include the specific term.

The term “cycloalkyl” as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term “heterocycloalkyl” is a type of cycloalkyl group as defined above, and is included within the meaning of the term “cycloalkyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

The term “polyalkylene group” as used herein is a group having two or more CH₂ groups linked to one another. The polyalkylene group can be represented by the formula —(CH₂)_a—, where “a” is an integer of from 2 to 500.

The terms “alkoxy” and “alkoxyl” as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an “alkoxy” group can be defined as —OA¹ where A¹ is alkyl or cycloalkyl as defined above. “Alkoxy” also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as —OA¹-OA² or —OA¹-(OA²)_a-OA³, where “a” is an integer of from 1 to 200 and A¹, A², and A³ are alkyl and/or cycloalkyl groups.

The term “alkenyl” as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond.

Asymmetric structures such as (A¹A²)C=C(A³A⁴) are intended to include both the E and Z isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

The term “cycloalkenyl” as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bond, i.e., C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term “heterocycloalkenyl” is a type of cycloalkenyl group as defined above, and is included within the meaning of the term “cycloalkenyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be

substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

The term “alkynyl” as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

The term “cycloalkynyl” as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bond. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononyl, and the like. The term “heterocycloalkynyl” is a type of cycloalkenyl group as defined above, and is included within the meaning of the term “cycloalkynyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

The term “aromatic group” as used herein refers to a ring structure having cyclic clouds of delocalized π electrons above and below the plane of the molecule, where the π clouds contain (4n+2) π electrons. A further discussion of aromaticity is found in Morrison and Boyd, Organic Chemistry, (5th Ed., 1987), Chapter 13, entitled “Aromaticity,” pages 477-497, incorporated herein by reference. The term “aromatic group” is inclusive of both aryl and heteroaryl groups.

The term “aryl” as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, anthracene, and the like. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, —NH₂, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term “biaryl” is a specific type of aryl group and is included in the definition of “aryl.” In addition, the aryl group can be a single ring structure or comprise multiple ring structures that are either fused ring structures or attached via one or more bridging groups such as a carbon-carbon bond. For example, biaryl can be two aryl groups that are bound together via a fused ring structure, as in naphthalene, or are attached via one or more carbon-carbon bonds, as in biphenyl.

The term “aldehyde” as used herein is represented by the formula —C(O)H. Throughout this specification “C(O)” is a short hand notation for a carbonyl group, i.e., C=O.

The terms “amine” or “amino” as used herein are represented by the formula —NA¹A², where A¹ and A² can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl,

cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. A specific example of amino is —NH_2 .

The term “alkylamino” as used herein is represented by the formula —NH(—alkyl) where alkyl is as described herein. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl) amino group, hexylamino group, and the like.

The term “dialkylamino” as used herein is represented by the formula —N(—alkyl)_2 where alkyl is as described herein. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group and the like.

The term “carboxylic acid” as used herein is represented by the formula —C(O)OH .

The term “ester” as used herein is represented by the formula —OC(O)A^1 or —C(O)OA^1 , where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term “polyester” as used herein is represented by the formula $\text{—(A}^1\text{O(O)C—A}^2\text{—C(O)O)}_a\text{—}$ or $\text{—(A}^1\text{O(O)C—A}^2\text{—OC(O))}_a\text{—}$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and “a” is an integer from 1 to 500. “Polyester” is as the term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

The term “ether” as used herein is represented by the formula A^1OA^2 , where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term “polyether” as used herein is represented by the formula $\text{—(A}^1\text{O—A}^2\text{O)}_a\text{—}$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and “a” is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

The terms “halo,” “halogen,” or “halide” as used herein can be used interchangeably and refer to F, Cl, Br, or I.

The terms “pseudohalide,” “pseudohalogen,” or “pseudohalo” as used herein can be used interchangeably and refer to functional groups that behave substantially similar to halides. Such functional groups include, by way of example, cyano, thiocyanato, azido, trifluoromethyl, trifluoromethoxy, perfluoroalkyl, and perfluoroalkoxy groups.

The term “heteroalkyl” as used herein refers to an alkyl group containing at least one heteroatom. Suitable heteroatoms include, but are not limited to, O, N, Si, P and S, wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. Heteroalkyls can be substituted as defined above for alkyl groups.

The term “heteroaryl” as used herein refers to an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus, where N-oxides, sulfur oxides, and dioxides are

permissible heteroatom substitutions. The heteroaryl group can be substituted or unsubstituted. The heteroaryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein. Heteroaryl groups can be monocyclic, or alternatively fused ring systems. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridinyl, pyrrolyl, N-methylpyrrolyl, quinolinyl, isoquinolinyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridazinyl, pyrazinyl, benzofuranyl, benzodioxolyl, benzothiophenyl, indolyl, indazolyl, benzimidazolyl, imidazopyridinyl, pyrazolopyridinyl, and pyrazolopyrimidinyl.

Further not limiting examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, benzo[d]oxazolyl, benzo[d]thiazolyl, quinolinyl, quinazolinyl, indazolyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazolyl, and pyrido[2,3-b]pyrazinyl.

The terms “heterocycle” or “heterocyclyl” as used herein can be used interchangeably and refer to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Thus, the term is inclusive of, but not limited to, “heterocycloalkyl,” “heteroaryl,” “bicyclic heterocycle,” and “polycyclic heterocycle.” Heterocycle includes pyridine, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, thiadiazole, including 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridazine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like. The term heterocyclyl group can also be a C2 heterocyclyl, C2-C3 heterocyclyl, C2-C4 heterocyclyl, C2-C5 heterocyclyl, C2-C6 heterocyclyl, C2-C7 heterocyclyl, C2-C8 heterocyclyl, C2-C9 heterocyclyl, C2-C10 heterocyclyl, C2-CT 1 heterocyclyl, and the like up to and including a C2-C18 heterocyclyl. For example, a C2 heterocyclyl comprises a group which has two carbon atoms and at least one heteroatom, including, but not limited to, aziridinyl, diazetidinyl, dihydrodiazetyl, oxiranyl, thiiranyl, and the like. Alternatively, for example, a C5 heterocyclyl comprises a group that has five carbon atoms and at least one heteroatom, including, but not limited to, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, diazepanyl, pyridinyl, and the like. It is understood that a heterocyclyl group may be bound either through a heteroatom in the ring, where chemically possible, or one of carbons comprising the heterocyclyl ring.

The term “bicyclic heterocycle” or “bicyclic heterocyclyl” as used herein refers to a ring system in which at least one of the ring members is other than carbon. Bicyclic heterocyclyl encompasses ring systems wherein an aromatic ring is fused with another aromatic ring, or wherein an aromatic ring is fused with a non-aromatic ring. Bicyclic heterocyclyl encompasses ring systems wherein a benzene ring is fused to a 5- or a 6-membered ring containing 1, 2, or 3 ring heteroatoms or wherein a pyridine ring is fused to a 5- or a 6-membered ring containing 1, 2, or 3 ring heteroatoms. Bicyclic heterocyclic groups include, but are not limited to, indolyl, indazolyl, pyrazolo[1,5-a]pyridinyl, benzofuranyl, quinolinyl, quinoxalinyl, 1,3-benzodioxolyl,

2,3-dihydro-1,4-benzodioxinyl, 3,4-dihydro-2H-chromenyl, 1H-pyrazolo[4,3-c]pyridin-3-yl; 1H-pyrrolo[3,2-b]pyridin-3-yl; and 1H-pyrazolo[3,2-b]pyridin-3-yl.

The term "heterocycloalkyl" as used herein refers to an aliphatic, partially unsaturated or fully saturated, 3- to 14-membered ring system, including single rings of 3 to 8 atoms and bi- and tricyclic ring systems. The heterocycloalkyl ring-systems include one to four heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein a nitrogen and sulfur heteroatom optionally can be oxidized and a nitrogen heteroatom optionally can be substituted. Representative heterocycloalkyl groups include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

The term "hydroxyl" or "hydroxy" as used herein is represented by the formula —OH.

The term "ketone" as used herein is represented by the formula $A^1C(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

The term "azide" or "azido" as used herein is represented by the formula —N₃.

The term "nitro" as used herein is represented by the formula —NO₂.

The term "nitrile" or "cyano" as used herein is represented by the formula —CN.

The term "silyl" as used herein is represented by the formula —SiA¹A²A³, where A¹, A², and A³ can be, independently, hydrogen or an alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

The term "sulfo-oxo" as used herein is represented by the formulas —S(O)A¹, —S(O)₂A¹, —OS(O)₂A¹, or —OS(O)₂OA¹, where A¹ can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification "S(O)" is a short hand notation for S=O. The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by the formula —S(O)₂A¹, where A¹ can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfone" as used herein is represented by the formula A¹S(O)₂A², where A¹ and A² can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfoxide" as used herein is represented by the formula A¹S(O)A², where A¹ and A² can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

The term "thiol" as used herein is represented by the formula —SH.

"R¹," "R²," "R³," "Rⁿ," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R¹ is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (i.e., attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group.

The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogen of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; —(CH₂)₀₋₄R[○]; —(CH₂)₀₋₄OR[○]; —O(CH₂)₀₋₄R[○]; —O—(CH₂)₀₋₄C(O)OR[○]; —(CH₂)₀₋₄CH(OR[○])₂; —(CH₂)₀₋₄SR[○]; —(CH₂)₀₋₄Ph, which may be substituted with R[○]; —(CH₂)₀₋₄O(CH₂)₀₋₁Ph which may be substituted with R[○]; —CH=CHPh, which may be substituted with R[○]; —(CH₂)₀₋₄O(CH₂)₀₋₁-pyridyl which may be substituted with R[○]; —NO₂; —CN; —N₃; —(CH₂)₀₋₄N(R[○])₂; —(CH₂)₀₋₄N(R[○])C(O)R[○]; —N(R[○])C(S)R[○]; —(CH₂)₀₋₄N(R[○])C(O)NR[○]₂; —N(R[○])C(S)NR[○]₂; —(CH₂)₀₋₄N(R[○])C(O)OR[○]; —N(R[○])N(R[○])C(O)R[○]; —N(R[○])N(R[○])C(O)NR[○]₂; —N(R[○])N(R[○])C(O)OR[○]; —(CH₂)₀₋₄C(O)R[○]; —C(S)R[○]; —(CH₂)₀₋₄C(O)OR[○]; —(CH₂)₀₋₄C(O)SR[○]; —(CH₂)₀₋₄C(O)OSiR[○]₃; —(CH₂)₀₋₄OC(O)R[○]; —OC(O)(CH₂)₀₋₄SR[○]; —SC(S)SR[○]; —(CH₂)₀₋₄SC(O)R[○]; —(CH₂)₀₋₄C(O)NR[○]₂; —C(S)NR[○]₂; —C(S)SR[○]; —(CH₂)₀₋₄OC(O)NR[○]₂; —C(O)N(OR[○])R[○]; —C(O)C(O)R[○]; —C(O)CH₂C(O)R[○]; —C(NOR[○])R[○]; —(CH₂)₀₋₄SSR[○]; —(CH₂)₀₋₄S(O)₂R[○]; —(CH₂)₀₋₄S(O)₂OR[○]; —(CH₂)₀₋₄OS(O)₂R[○]; —S(O)₂NR[○]₂; —(CH₂)₀₋₄S(O)R[○]; —N(R[○])S(O)₂NR[○]₂; —N(R[○])S(O)₂R[○]; —N(OR[○])R[○]; —C(NH)NR[○]₂; —P(O)₂R[○]; —P(O)R[○]₂; —OP(O)R[○]₂; —OP(O)(OR[○])₂; SiR[○]₃; —(C₁₋₄ straight or branched alkylene)O—N(R[○])₂; or —(C₁₋₄ straight or branched alkylene)C(O)O—N(R[○])₂, wherein each R[○] may be substituted as defined below and is independently hydrogen, C1-6 aliphatic, —CH₂Ph, —O(CH₂)₀₋₁Ph, —CH₂-(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R[○], taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R[○] (or the ring formed by taking two independent occurrences of R[○] together with their intervening atoms), are independently halogen, —(CH₂)₀₋₂R[●], —(haloR[●]), —(CH₂)₀₋₂OH,

$-(\text{CH}_2)_{0-2}\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{CH}(\text{OR}^\bullet)_2$; $-\text{O}(\text{haloR}^\bullet)$,
 $-\text{CN}$, $-\text{N}_3$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{R}^\bullet$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OH}$,
 $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SH}$,
 $-(\text{CH}_2)_{0-2}\text{NH}_2$, $-(\text{CH}_2)_{0-2}\text{NHR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{NR}^\bullet_2$,
 $-\text{NO}_2$, $-\text{SiR}^\bullet_3$, $-\text{OSiR}^\bullet_3$, $-\text{C}(\text{O})\text{SR}^\bullet$, $-(\text{C}_{1-4}$ straight
 or branched alkylene) $\text{C}(\text{O})\text{OR}^\bullet$, or $-\text{SSR}^\bullet$ wherein each
 R^\bullet is unsubstituted or where preceded by "halo" is substi-
 tuted only with one or more halogens, and is independently
 selected from C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a
 5-6-membered saturated, partially unsaturated, or aryl ring
 having 0-4 heteroatoms independently selected from nitro-
 gen, oxygen, or sulfur. Suitable divalent substituents on a
 saturated carbon atom of R° include $=\text{O}$ and $=\text{S}$.

Suitable divalent substituents on a saturated carbon atom
 of an "optionally substituted" group include the following:
 $=\text{O}$, $=\text{S}$, $=\text{NNR}^*_2$, $=\text{NNHC}(\text{O})\text{R}^*$, $=\text{NNHC}(\text{O})\text{OR}^*$,
 $=\text{NNHS}(\text{O})_2\text{R}^*$, $=\text{NR}^*$, $=\text{NOR}^*$, $-\text{O}(\text{C}(\text{R}^*_2))_{2-3}\text{O}-$, or
 $-\text{S}(\text{C}(\text{R}^*_2))_{2-3}\text{S}-$, wherein each independent occurrence
 of R^* is selected from hydrogen, C_{1-6} aliphatic which may
 be substituted as defined below, or an unsubstituted 5-6-
 membered saturated, partially unsaturated, or aryl ring hav-
 ing 0-4 heteroatoms independently selected from nitrogen,
 oxygen, or sulfur. Suitable divalent substituents that are
 bound to vicinal substitutable carbons of an "optionally
 substituted" group include: $-\text{O}(\text{CR}^*_2)_{2-3}\text{O}-$, wherein each
 independent occurrence of R^* is selected from hydrogen,
 C_{1-6} aliphatic which may be substituted as defined below, or
 an unsubstituted 5-6-membered saturated, partially unsatu-
 rated, or aryl ring having 0-4 heteroatoms independently
 selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of R^\bullet include
 halogen, $-\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{haloR}^\bullet)$,
 $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$,
 $-\text{NR}^\bullet_2$, or $-\text{NO}_2$, wherein each R^\bullet is unsubstituted or
 where preceded by "halo" is substituted only with one or
 more halogens, and is independently C_{1-4} aliphatic,
 $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5-6-membered saturated,
 partially unsaturated, or aryl ring having 0-4 heteroatoms
 independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an
 "optionally substituted" group include $-\text{R}^\dagger$, $-\text{NR}^\dagger_2$,
 $-\text{C}(\text{O})\text{R}^\dagger$, $-\text{C}(\text{O})\text{OR}^\dagger$, $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^\dagger$, $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})$
 R^\dagger , $-\text{S}(\text{O})_2\text{R}^\dagger$, $-\text{S}(\text{O})_2\text{NR}^\dagger_2$, $-\text{C}(\text{S})\text{NR}^\dagger_2$, $-\text{C}(\text{NH})\text{NR}^\dagger_2$,
 or $-\text{N}(\text{R}^\dagger)\text{S}(\text{O})_2\text{R}^\dagger$; wherein each R^\dagger is independently
 hydrogen, C_{1-6} aliphatic which may be substituted as defined
 below, unsubstituted $-\text{OPh}$, or an unsubstituted 5-6-mem-
 bered saturated, partially unsaturated, or aryl ring having 0-4
 heteroatoms independently selected from nitrogen, oxygen,
 or sulfur, or, notwithstanding the definition above, two
 independent occurrences of R^\dagger , taken together with their
 intervening atom(s) form an unsubstituted 3-12-membered
 saturated, partially unsaturated, or aryl mono- or bicyclic
 ring having 0-4 heteroatoms independently selected from
 nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of R^\dagger are
 independently halogen, $-\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$,
 $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$,
 $-\text{NHR}^\bullet$, $-\text{NR}^\bullet_2$, or $-\text{NO}_2$, wherein each R^\bullet is unsub-
 stituted or where preceded by "halo" is substituted only with
 one or more halogens, and is independently C_{1-4} aliphatic,
 $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5-6-membered saturated,
 partially unsaturated, or aryl ring having 0-4 heteroatoms
 independently selected from nitrogen, oxygen, or sulfur.

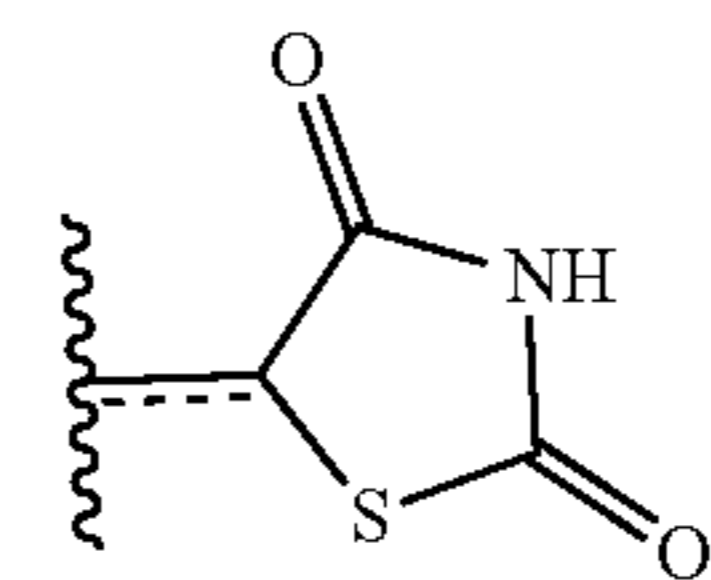
The term "leaving group" refers to an atom (or a group of
 atoms) with electron withdrawing ability that can be dis-
 placed as a stable species, taking with it the bonding
 electrons. Examples of suitable leaving groups include

halides and sulfonate esters, including, but not limited to,
 triflate, mesylate, tosylate, and brosylate.

The terms "hydrolysable group" and "hydrolysable moi-
 ety" refer to a functional group capable of undergoing
 hydrolysis, e.g., under basic or acidic conditions. Examples
 of hydrolysable residues include, without limitation, acid
 halides, activated carboxylic acids, and various protecting
 groups known in the art (see, for example, "Protective
 Groups in Organic Synthesis," T. W. Greene, P. G. M. Wuts,
 Wiley-Interscience, 1999).

The term "organic residue" defines a carbon-containing
 residue, i.e., a residue comprising at least one carbon atom,
 and includes but is not limited to the carbon-containing
 groups, residues, or radicals defined hereinabove. Organic
 residues can contain various heteroatoms, or be bonded to
 another molecule through a heteroatom, including oxygen,
 nitrogen, sulfur, phosphorus, or the like. Examples of
 organic residues include but are not limited alkyl or substi-
 tuted alkyls, alkoxy or substituted alkoxy, mono or di-
 substituted amino, amide groups, etc. Organic residues can
 preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon
 atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6
 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an
 organic residue can comprise 2 to 18 carbon atoms, 2 to 15,
 carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2
 to 4 carbon atoms, or 2 to 4 carbon atoms.

A very close synonym of the term "residue" is the term
 "radical," which as used in the specification and concluding
 claims, refers to a fragment, group, or substructure of a
 molecule described herein, regardless of how the molecule
 is prepared. For example, a 2,4-thiazolidinedione radical in
 a particular compound has the structure:



regardless of whether thiazolidinedione is used to prepare
 the compound. In some embodiments the radical (for
 example an alkyl) can be further modified (i.e., substituted
 alkyl) by having bonded thereto one or more "substituent
 radicals." The number of atoms in a given radical is not
 critical to the present invention unless it is indicated to the
 contrary elsewhere herein.

"Organic radicals," as the term is defined and used herein,
 contain one or more carbon atoms. An organic radical can
 have, for example, 1-26 carbon atoms, 1-18 carbon atoms,
 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or
 1-4 carbon atoms. In a further aspect, an organic radical can
 have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon
 atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon
 atoms. Organic radicals often have hydrogen bound to at
 least some of the carbon atoms of the organic radical. One
 example, of an organic radical that comprises no inorganic
 atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some
 embodiments, an organic radical can contain 1-10 inorganic
 heteroatoms bound thereto or therein, including halogens,
 oxygen, sulfur, nitrogen, phosphorus, and the like. Examples
 of organic radicals include but are not limited to an alkyl,
 substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-
 substituted amino, di-substituted amino, acyloxy, cyano,
 carboxy, carboalkoxy, alkylcarboxamide, substituted alkyl-
 carboxamide, dialkylcarboxamide, substituted dialkylcar-

boxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, e.g., each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines (bonds to atoms below the plane). The Cahn-Ingold-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

When the disclosed compounds contain one chiral center, the compounds exist in two enantiomeric forms. Unless specifically stated to the contrary, a disclosed compound includes both enantiomers and mixtures of enantiomers, such as the specific 50:50 mixture referred to as a racemic mixture. The enantiomers can be resolved by methods known to those skilled in the art, such as formation of

diastereoisomeric salts which may be separated, for example, by crystallization (see, CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation by David Kozma (CRC Press, 2001)); formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step can liberate the desired enantiomeric form. Alternatively, specific enantiomers can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

Designation of a specific absolute configuration at a chiral carbon in a disclosed compound is understood to mean that the designated enantiomeric form of the compounds can be provided in enantiomeric excess (e.e.). Enantiomeric excess, as used herein, is the presence of a particular enantiomer at greater than 50%, for example, greater than 60%, greater than 70%, greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. In one aspect, the designated enantiomer is substantially free from the other enantiomer. For example, the "R" forms of the compounds can be substantially free from the "S" forms of the compounds and are, thus, in enantiomeric excess of the "S" forms. Conversely, "S" forms of the compounds can be substantially free of "R" forms of the compounds and are, thus, in enantiomeric excess of the "R" forms.

When a disclosed compound has two or more chiral carbons, it can have more than two optical isomers and can exist in diastereoisomeric forms. For example, when there are two chiral carbons, the compound can have up to four optical isomers and two pairs of enantiomers ((S,S)/(R,R) and (R,S)/(S,R)). The pairs of enantiomers (e.g., (S,S)/(R,R)) are mirror image stereoisomers of one another. The stereoisomers that are not mirror-images (e.g., (S,S) and (R,S)) are diastereomers. The diastereoisomeric pairs can be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Unless otherwise specifically excluded, a disclosed compound includes each diastereoisomer of such compounds and mixtures thereof.

The compounds according to this disclosure may form prodrugs at hydroxyl or amino functionalities using alkoxy, amino acids, etc., groups as the prodrug forming moieties. For instance, the hydroxymethyl position may form mono-, di- or triphosphates and again these phosphates can form prodrugs. Preparations of such prodrug derivatives are discussed in various literature sources (examples are: Alexander et al., J. Med. Chem. 1988, 31, 318; Aligas-Martin et al., PCT WO 2000/041531, p. 30). The nitrogen function converted in preparing these derivatives is one (or more) of the nitrogen atoms of a compound of the disclosure.

"Derivatives" of the compounds disclosed herein are pharmaceutically acceptable salts, prodrugs, deuterated forms, radioactively labeled forms, isomers, solvates and combinations thereof. The "combinations" mentioned in this context are refer to derivatives falling within at least two of the groups: pharmaceutically acceptable salts, prodrugs,

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deuterated forms, radioactively labeled forms, isomers, and solvates. Examples of radioactively labeled forms include compounds labeled with tritium, phosphorous-32, iodine-129, carbon-11, fluorine-18, and the like.

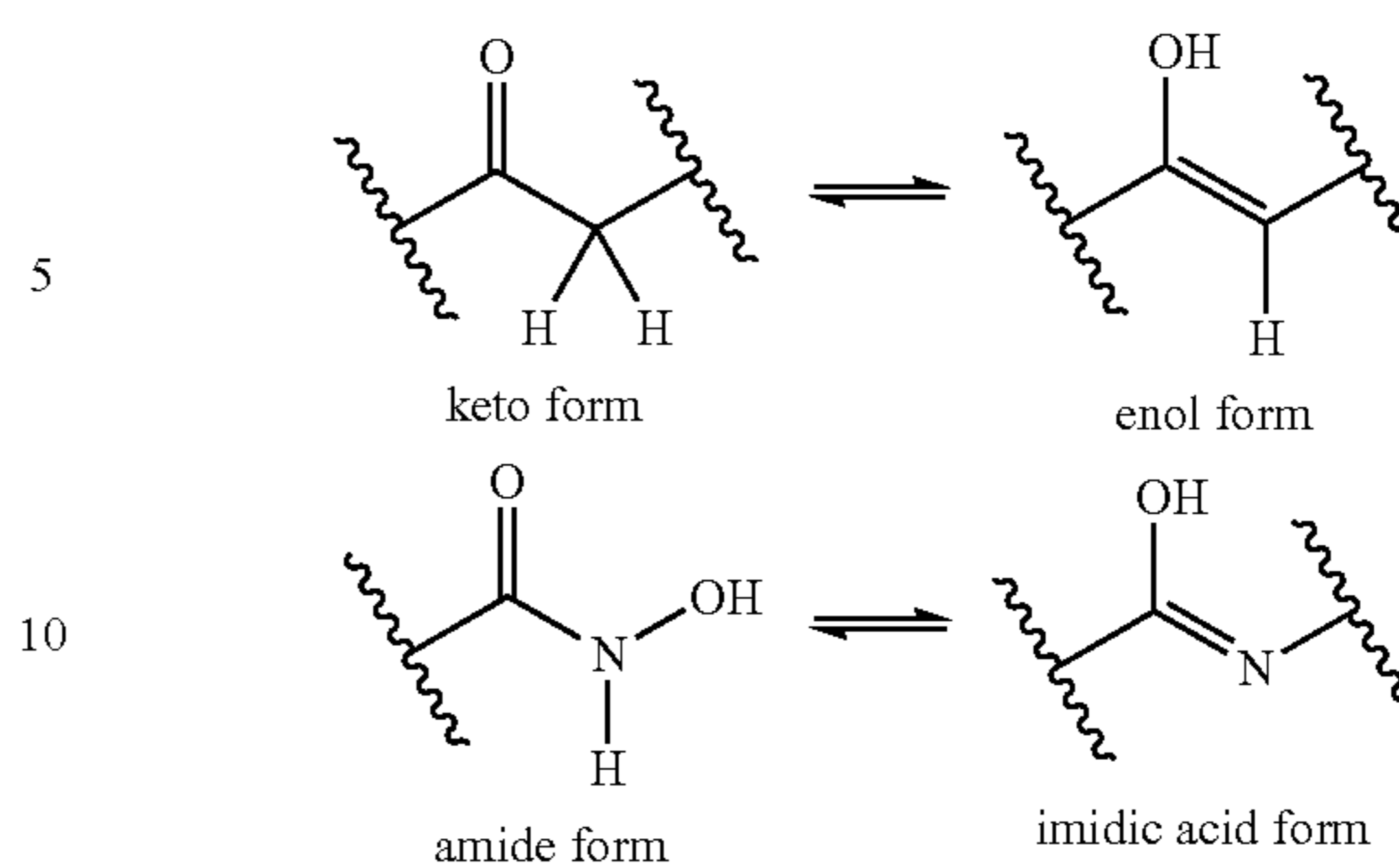
Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labeled or isotopically-substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvent or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

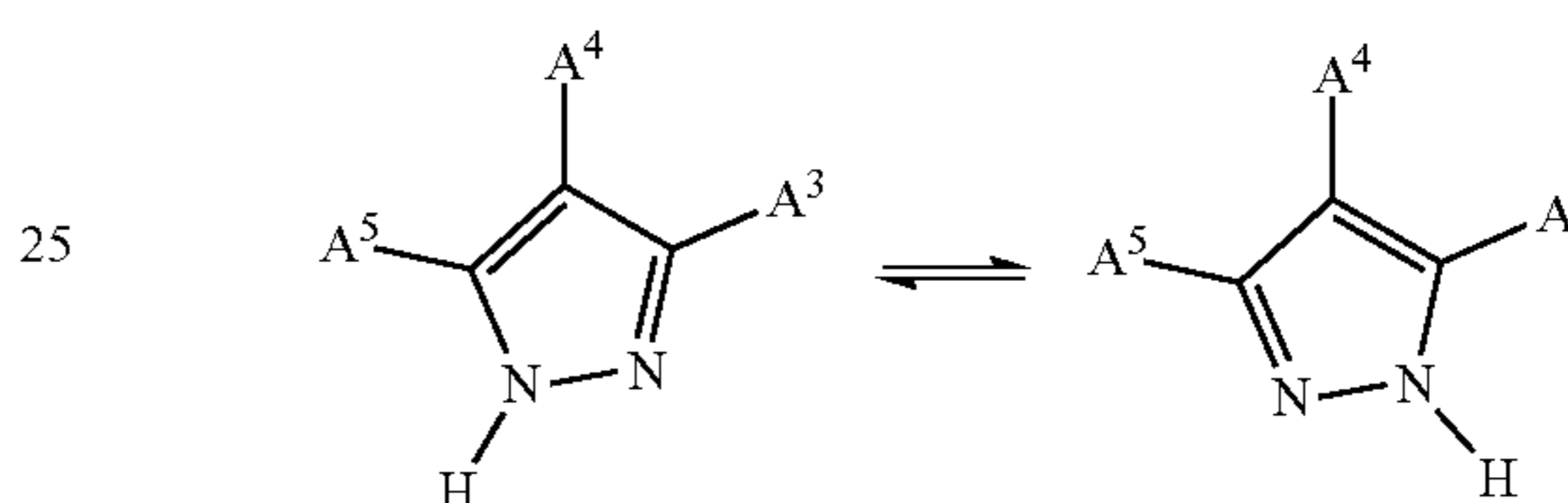
The term "co-crystal" means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrides or solvates, see e.g. "Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?" Almarason, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an α -hydrogen can exist in an equilibrium of the keto form and the enol form.

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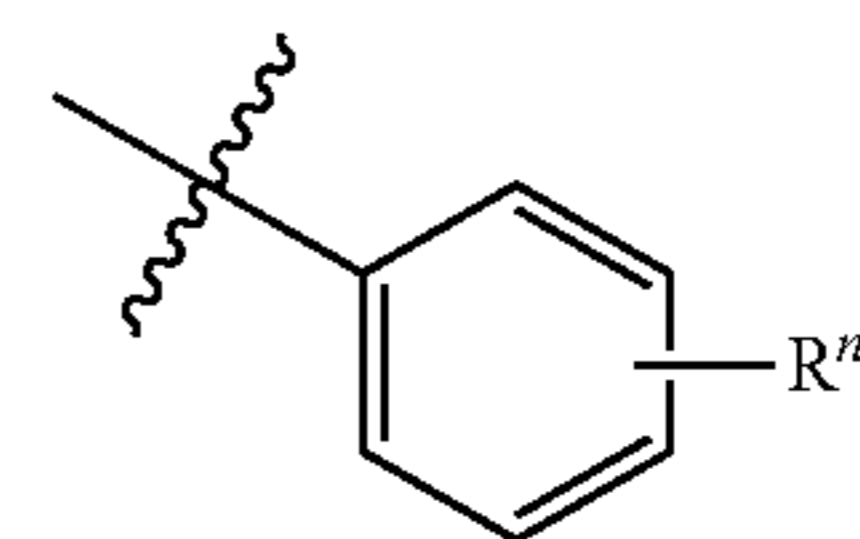
Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. As another example, pyrazoles can exist in two tautomeric forms, N^1 -unsubstituted, 3- A^3 and N^1 -unsubstituted, 5- A^3 as shown below.



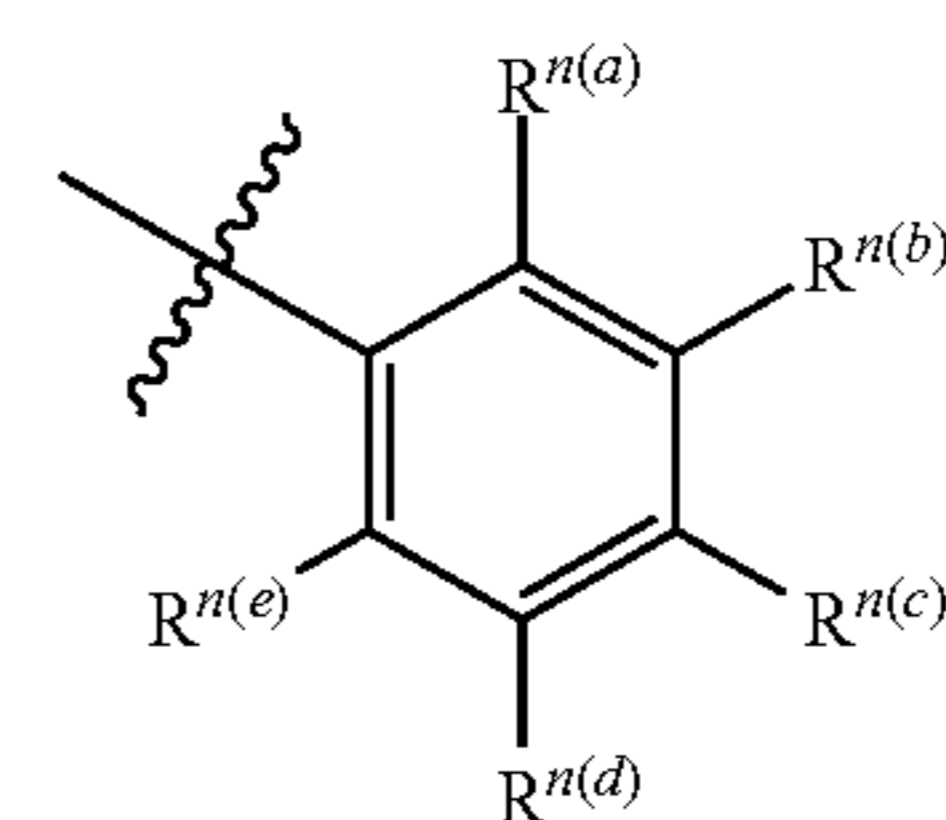
Unless stated to the contrary, the invention includes all such possible tautomers.

It is known that chemical substances form solids that are present in different states of order that are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

In some aspects, a structure of a compound can be represented by a formula:



which is understood to be equivalent to a formula:



wherein n is typically an integer. That is, R is understood to represent five independent substituents, $\text{R}^{n(a)}$, $\text{R}^{n(b)}$, $\text{R}^{n(c)}$, $\text{R}^{n(d)}$, $\text{R}^{n(e)}$. By "independent substituents," it is meant that each R substituent can be independently defined. For

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example, if in one instance $R^{n(a)}$ is halogen, then $R^{n(b)}$ is not necessarily halogen in that instance.

Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Acros Organics (Morris Plains, N.J.), Strem Chemicals (Newburyport, MA), Fisher Scientific (Pittsburgh, Pa.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and supplemental volumes (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

It is understood that the compounds and compositions disclosed herein have certain functions. Disclosed herein are

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certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

B. Compounds

In one aspect, the invention relates to compounds useful in treating disorders associated with a disorder of uncontrolled cellular proliferation such as, for example, cancers including, but not limited to, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

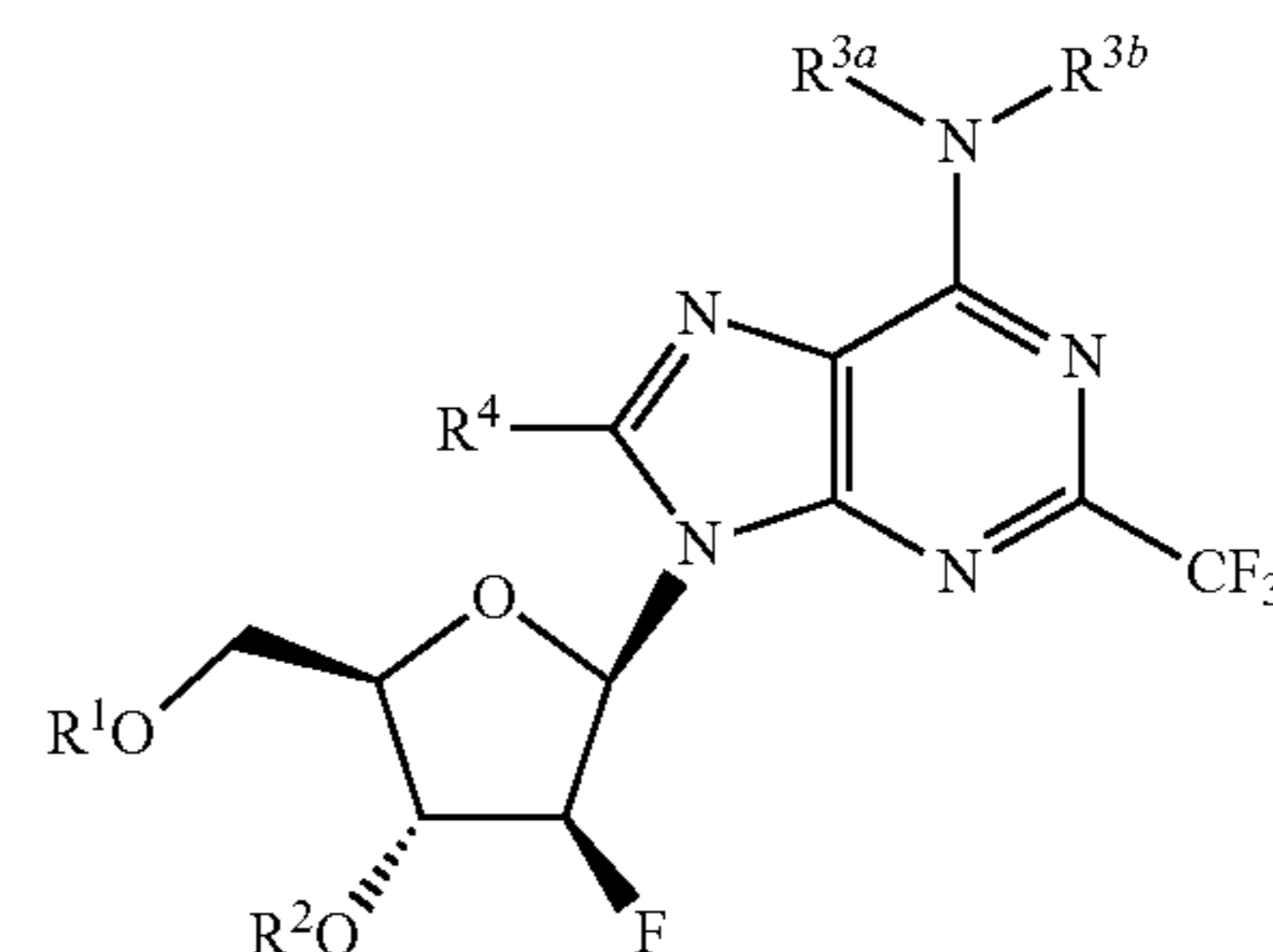
In a further aspect, the compound is a clofarabine analog.

In one aspect, the compounds of the invention are useful in the treatment of disorders of uncontrolled cellular proliferation, as further described herein.

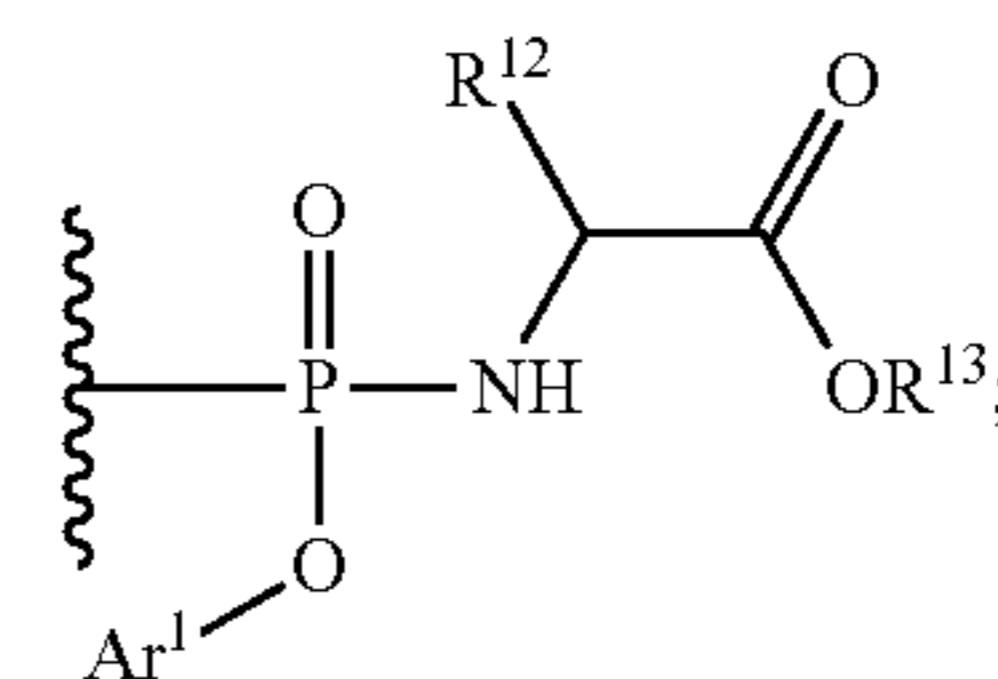
It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

1. Structure

In one aspect, the compound has a structure represented by a formula:



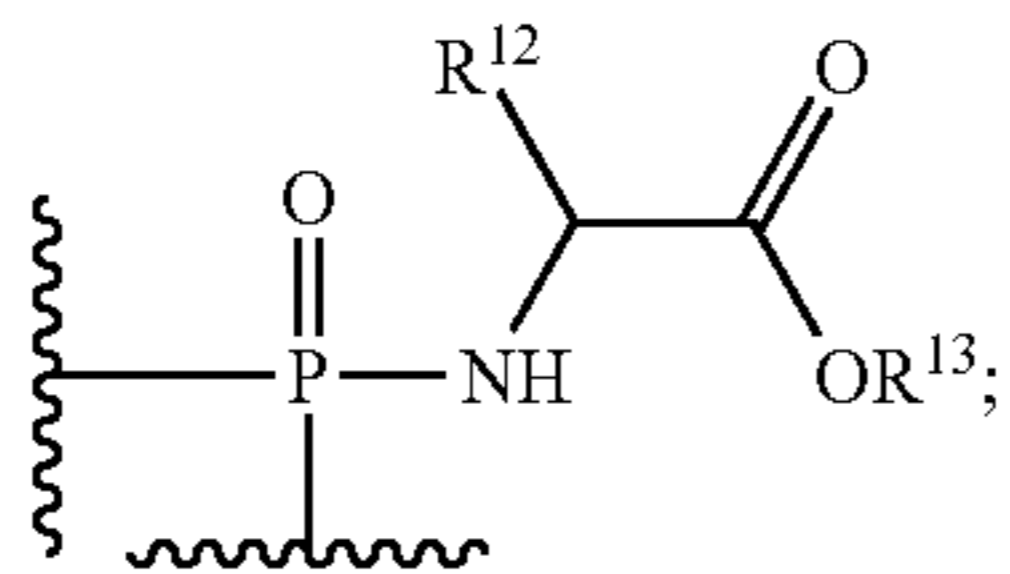
wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:



wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(C1-C8 \text{ alkyl})NHC(NH)NH_2$, $-(C1-C8 \text{ alkyl})CO_2H$, $-(C1-C8 \text{ alkyl})C(O)NH_2$, Cy^1 , and $-(C1-C8$

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alkyl)Cy¹; wherein Cy¹, when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R¹¹, when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, —(C1-C10 alkyl)CO₂(C1-C10 alkyl), —(C1-C10 alkyl)CO₂(C1-C10 alkylthiol), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar²; wherein Ar², when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R¹², when present, is selected from hydrogen and C1-C8 alkyl; wherein R¹³, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar³; wherein Ar³, when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar¹ is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R¹ and R² together comprise a structure represented by a formula:

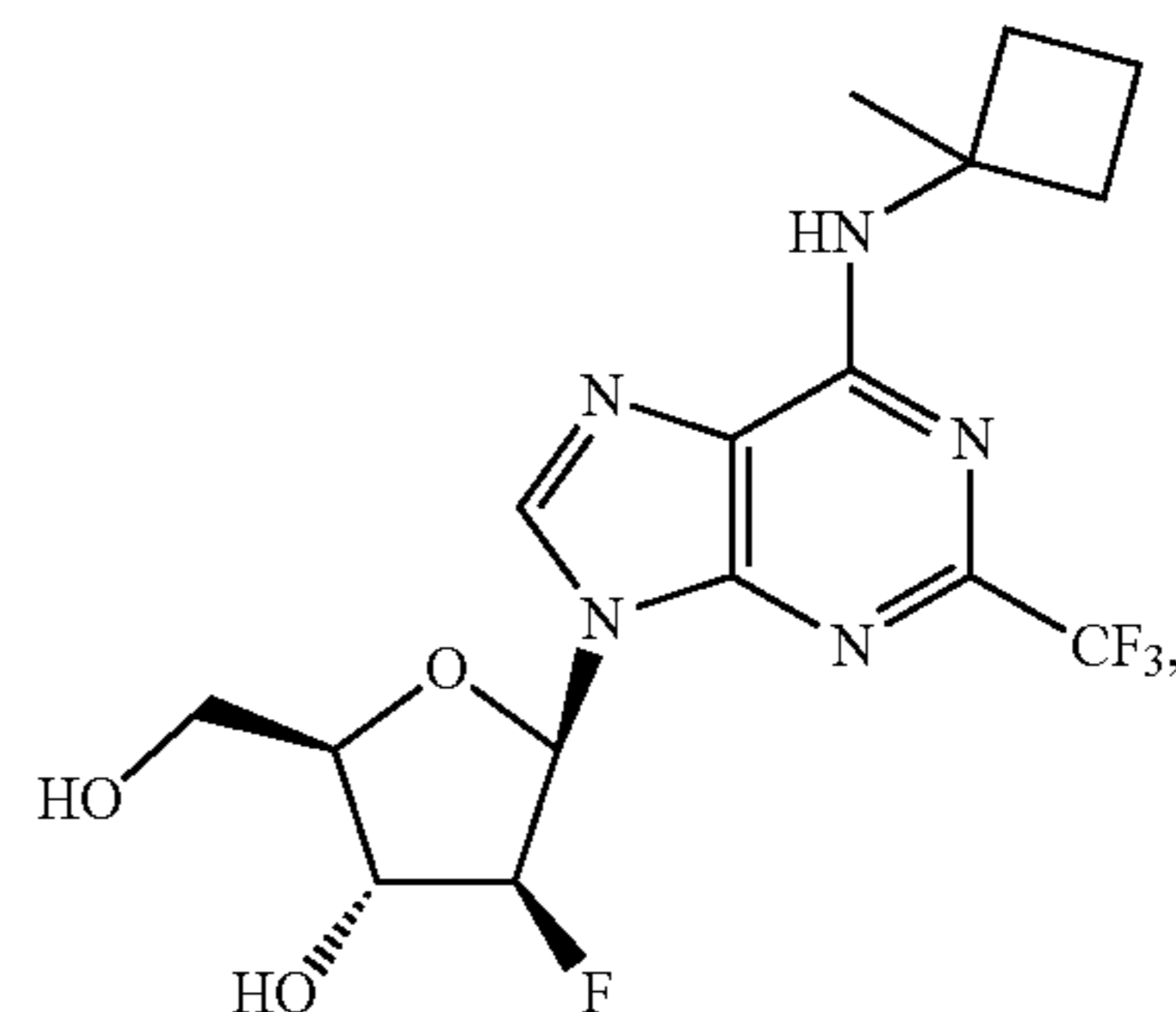
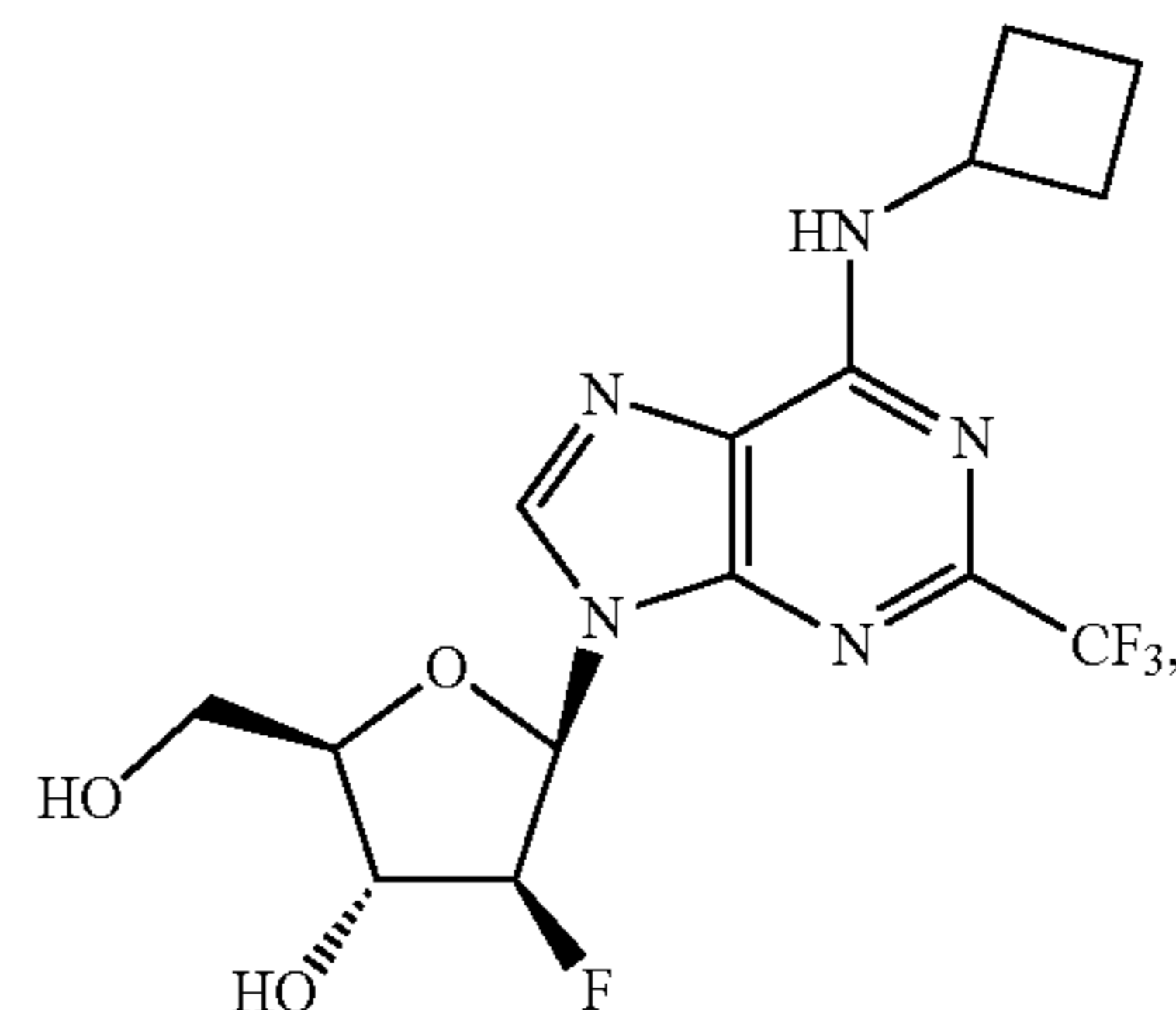
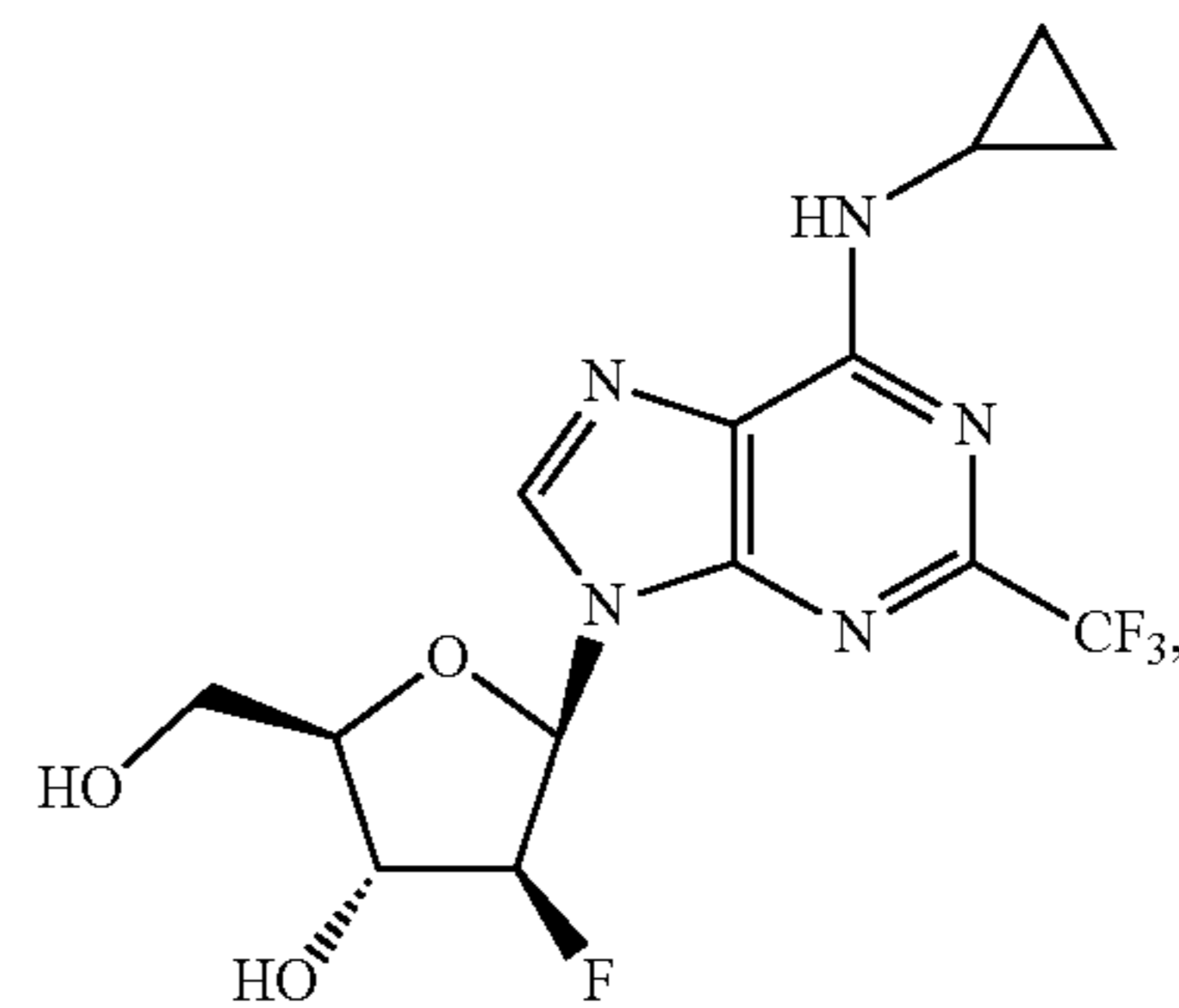
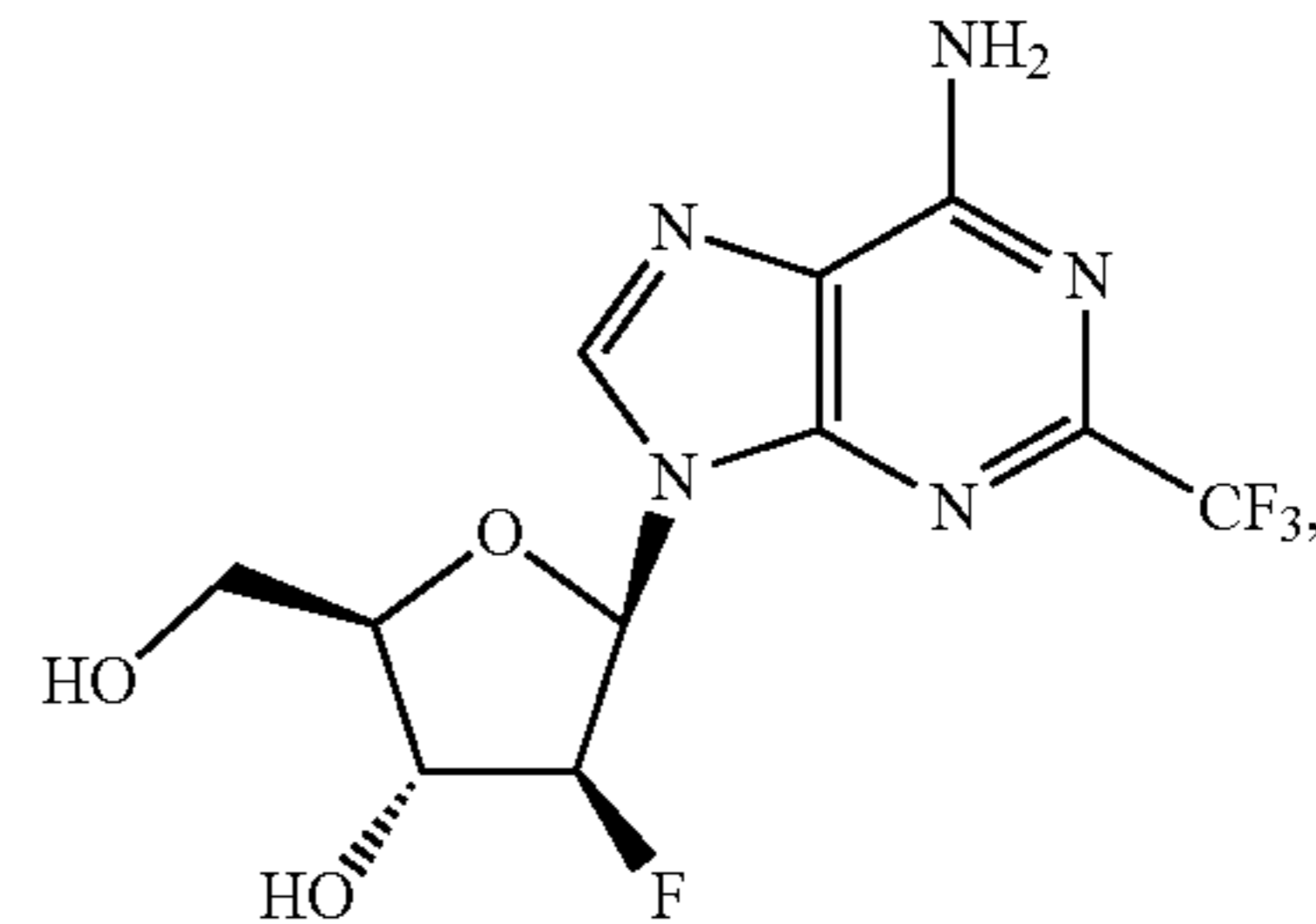


wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, C1-C12 alkyl, C1-C12 alkoxy, —C(O)R¹⁴, —(C1-C12 alkyl)CO₂H, and —(C1-C6 alkyl)Cy², provided that R^{3a} and R^{3b} are not simultaneously hydrogen; wherein R¹⁴, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH₂)R²¹; wherein R²¹, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, —(C1-C8 alkyl)NHC(NH)NH₂, —(C1-C8 alkyl)CO₂H, —(C1-C8 alkyl)C(O)NH₂, Cy³, and —(C1-C8 alkyl)Cy³; wherein Cy³, when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy², when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH,

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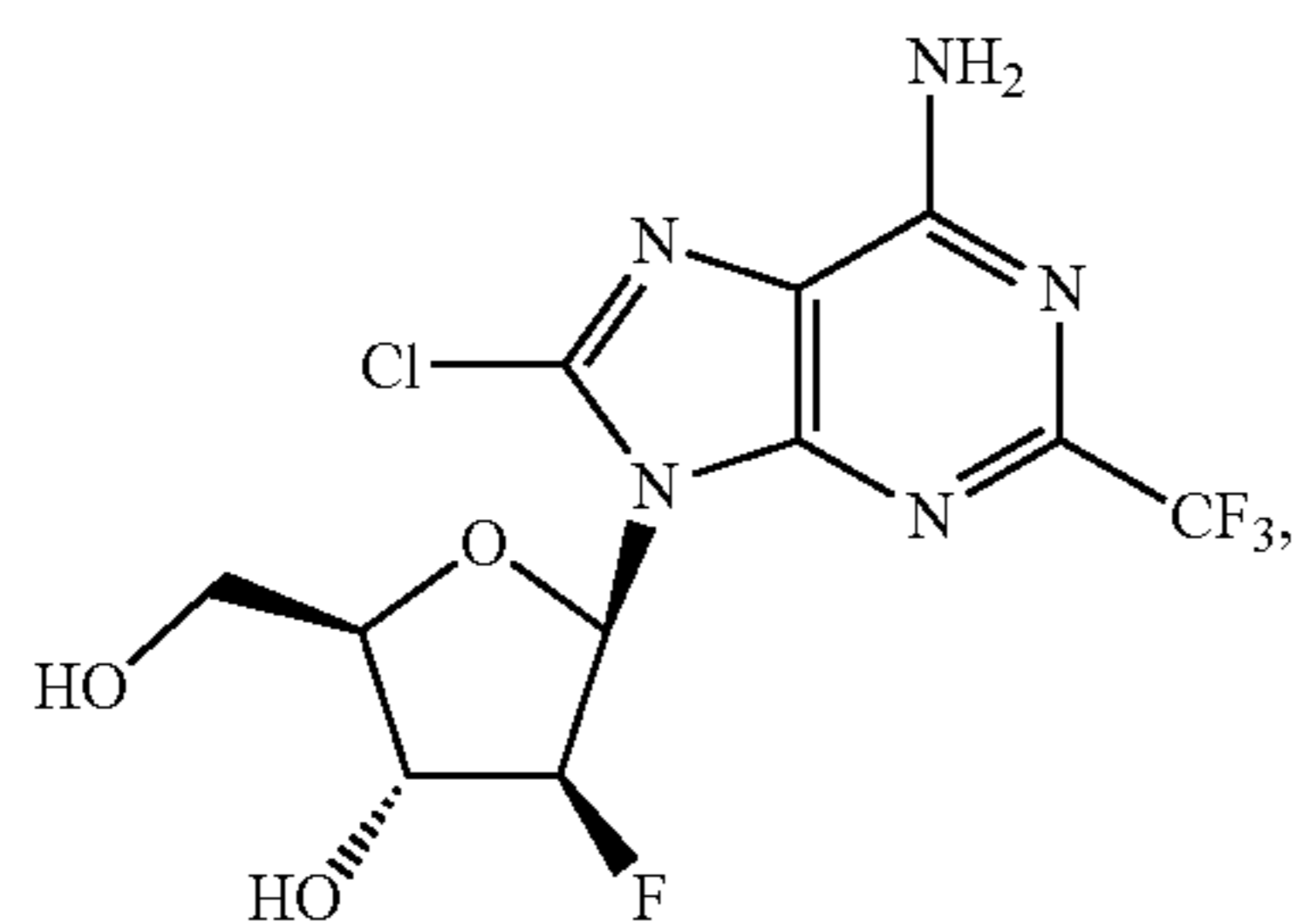
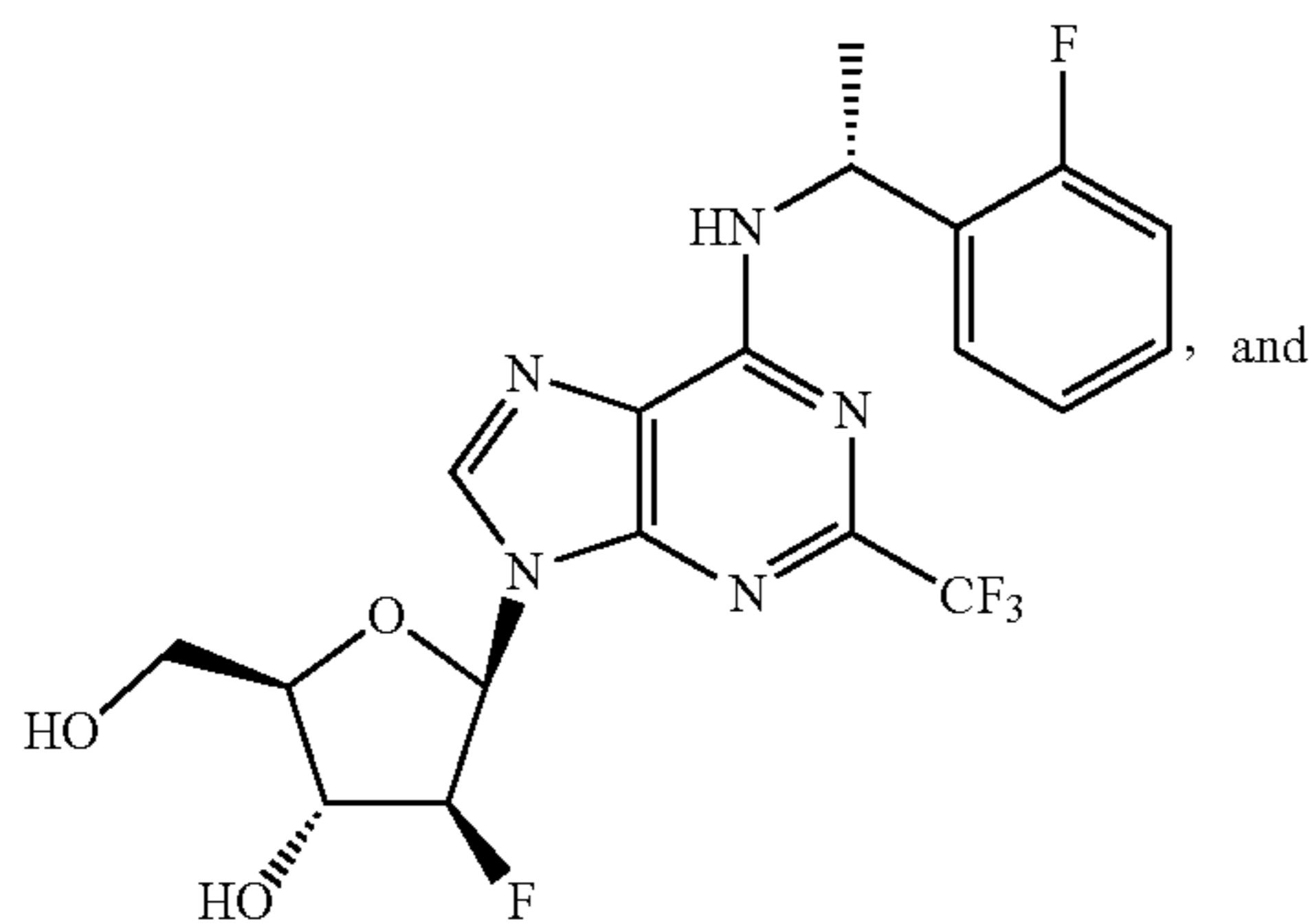
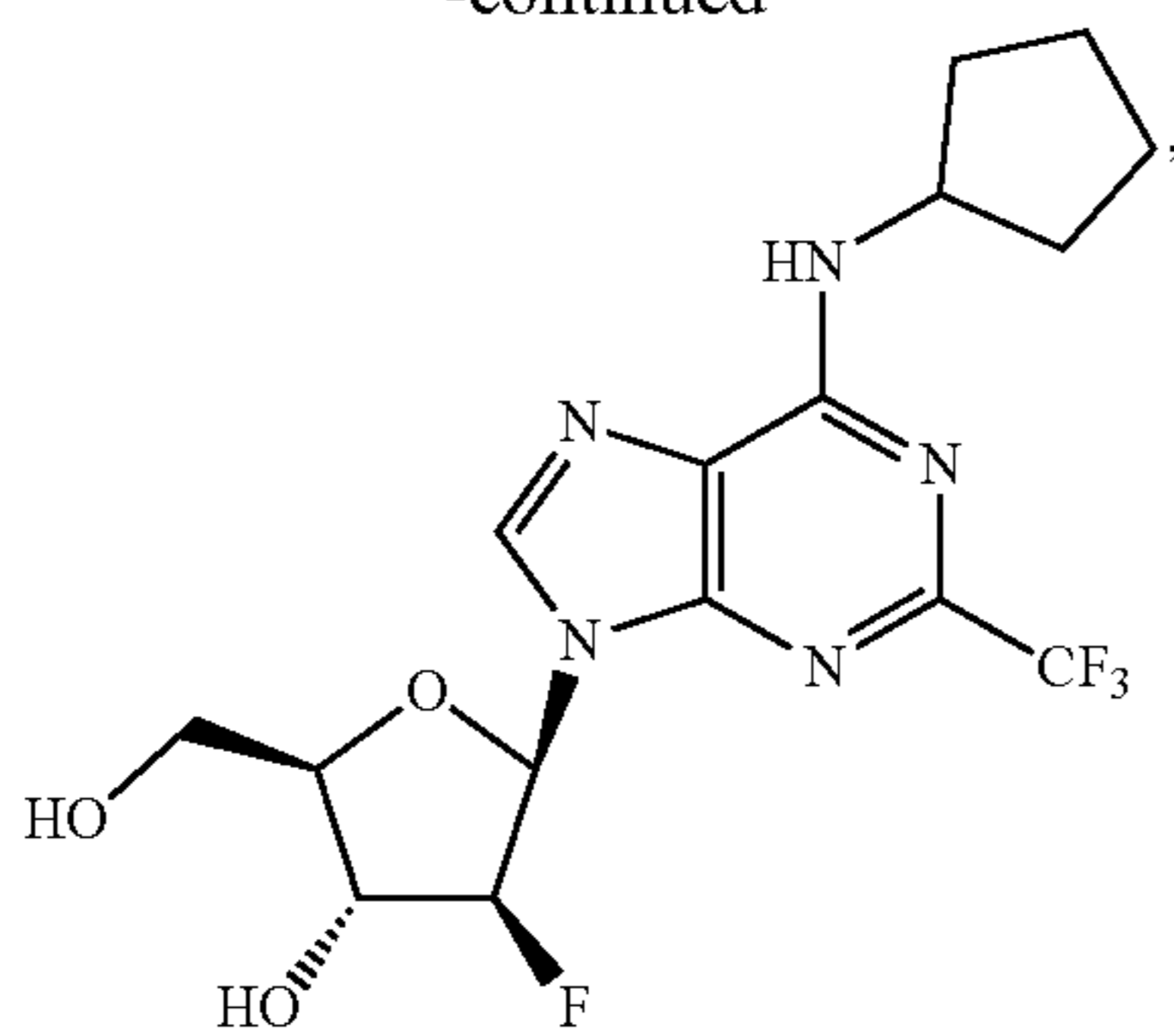
—NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R⁴ is hydrogen or chlorine, provided that when each of R¹ and R² is hydrogen, then at least one of R^{3a} and R^{3b} is a non-hydrogen group, and provided that when one of R^{3a} and R^{3b} is —(C1-C6 alkyl)Cy², then R¹ is hydrogen, or a pharmaceutically acceptable salt thereof.

In one aspect, the compound has a structure selected from:



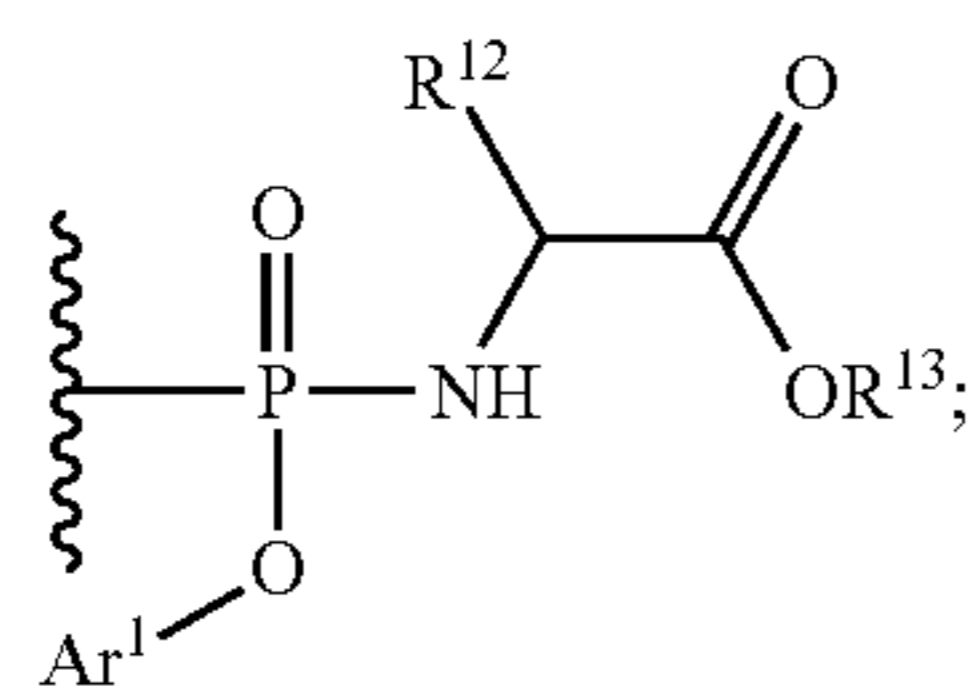
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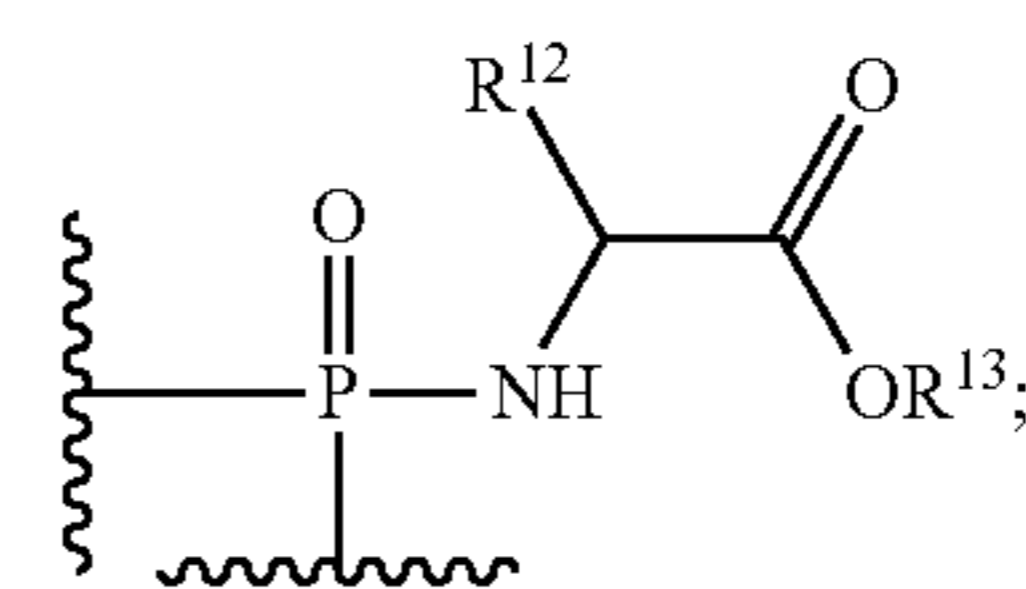
or a pharmaceutically acceptable salt thereof.

In various aspects, one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:



wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{20}$; wherein R^{20} , when present, is C1-C8 alkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, and Ar^2 ; wherein Ar^2 , when present, is unsubstituted C6 aryl; wherein R^{12} , when present, is C1-C8 alkyl; wherein R^{13} , when present, is C1-C10 alkyl; wherein Ar^1 is unsubstituted C6 aryl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:

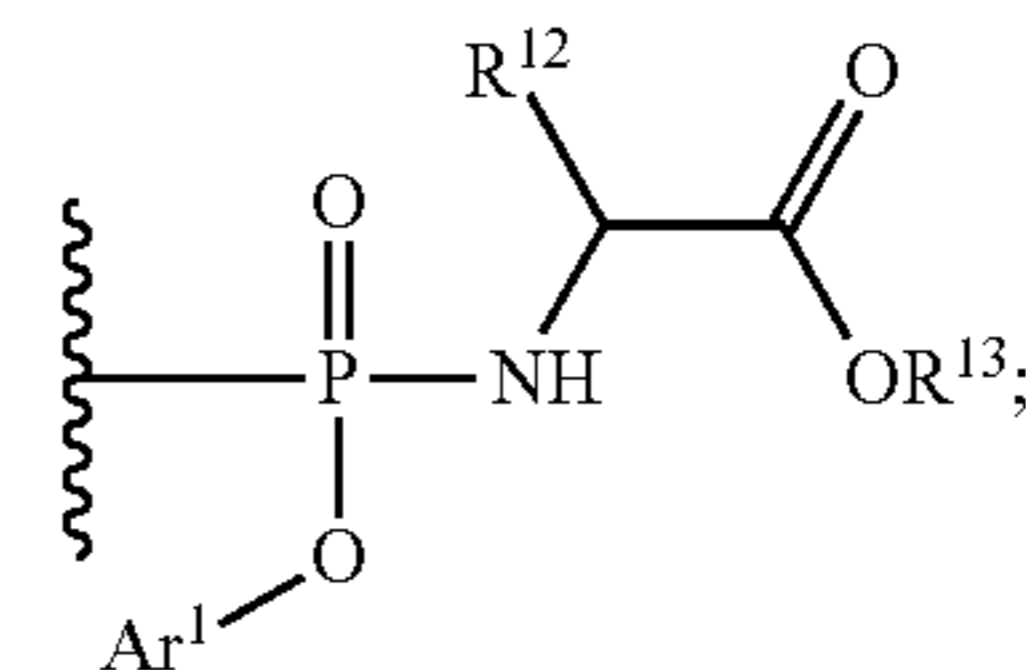
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and

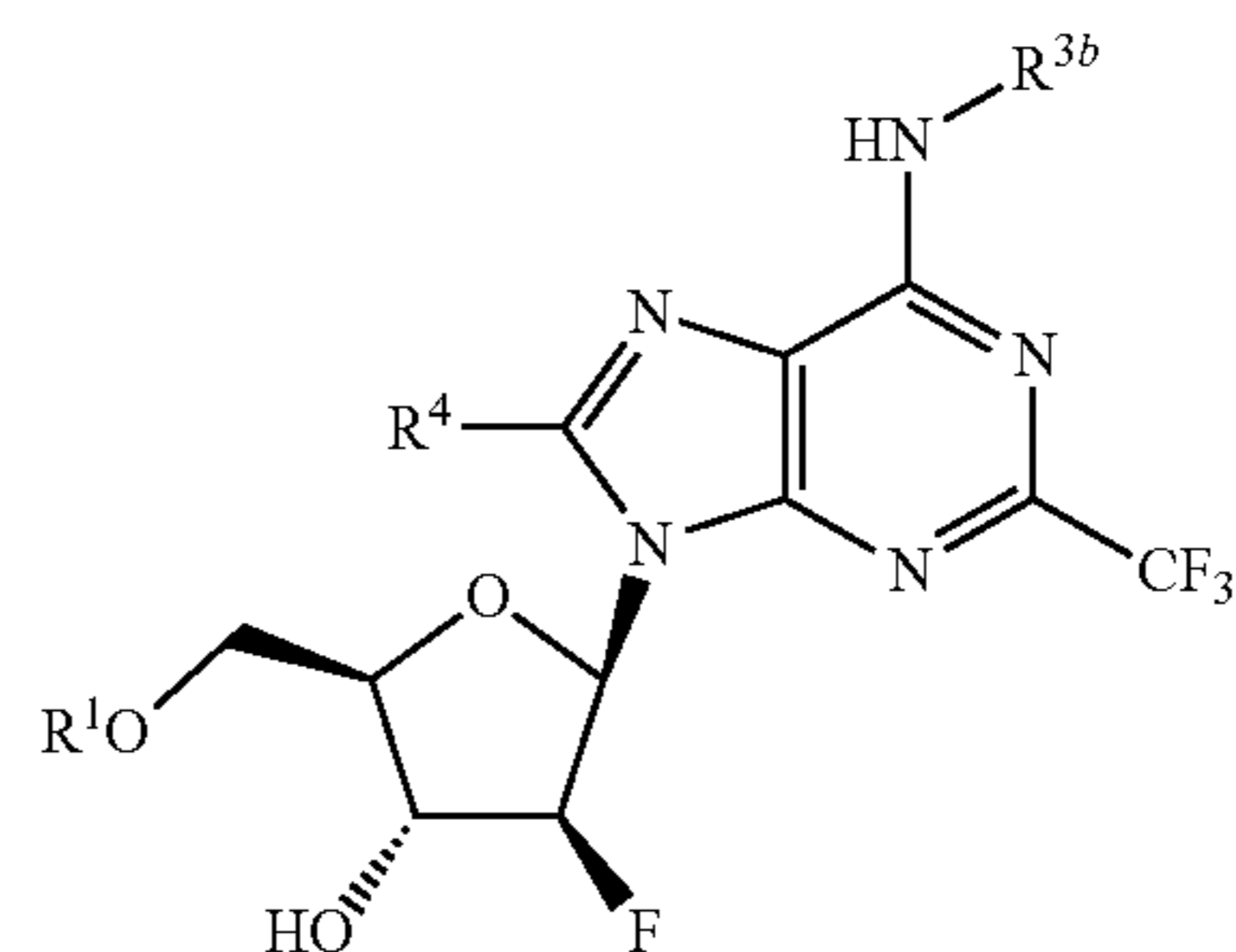
wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-OH$, C1-C12 alkyl, C1-C12 alkoxy, $-C(O)R^{14}$, $-(C1-C12\text{ alkyl})CO_2H$, and $-(C1-C6\text{ alkyl})Cy^2$, provided that R^{3a} and R^{3b} are not simultaneously hydrogen; wherein R^{14} , when present, is C1-C30 alkyl; wherein Cy^2 , when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine.

In various aspects, one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, and a structure represented by a formula:



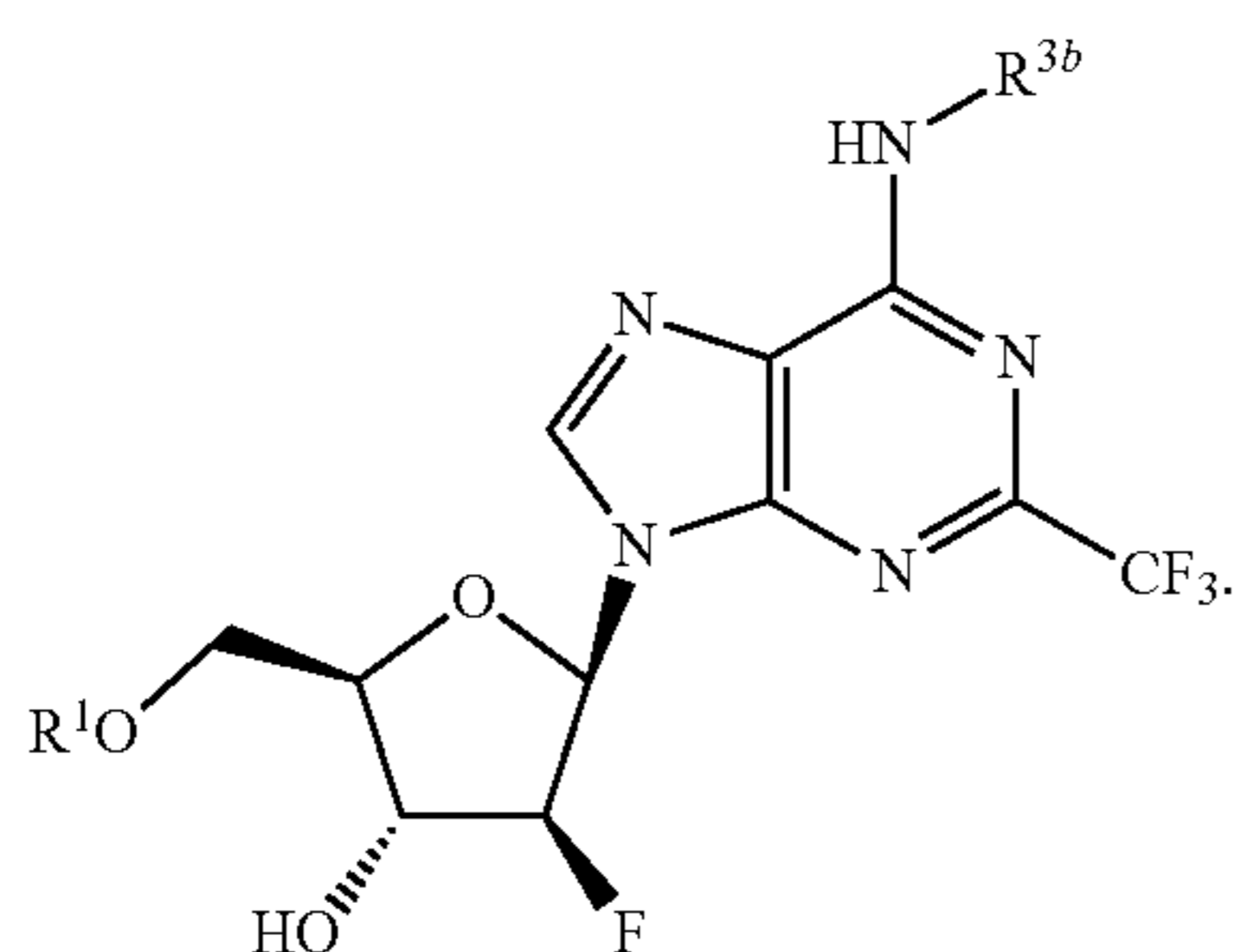
wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{20}$; wherein R^{20} , when present, is C1-C8 alkyl; wherein R^{12} , when present, is C1-C8 alkyl; wherein R^{13} , when present, is C1-C10 alkyl; wherein Ar^1 is unsubstituted C6 aryl; wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-OH$, C1-C12 alkyl, C1-C12 alkoxy, $-C(O)R^{14}$, $-(C1-C12\text{ alkyl})CO_2H$, and $-(C1-C6\text{ alkyl})Cy^2$, provided that R^{3a} and R^{3b} are not simultaneously hydrogen; wherein R^{14} , when present, is C1-C30 alkyl; wherein Cy^2 , when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine.

In various aspects, the compound has a structure represented by a formula:

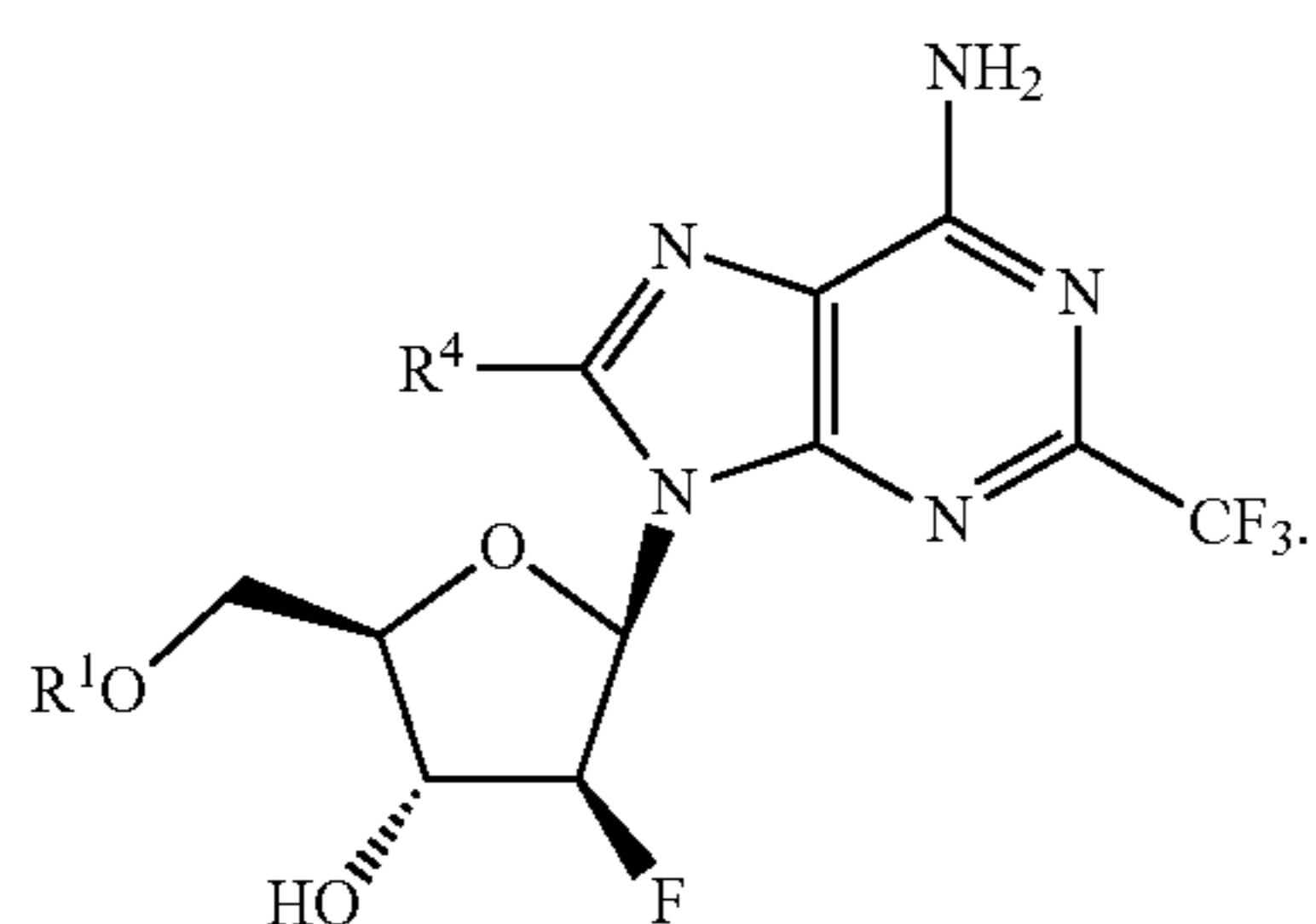


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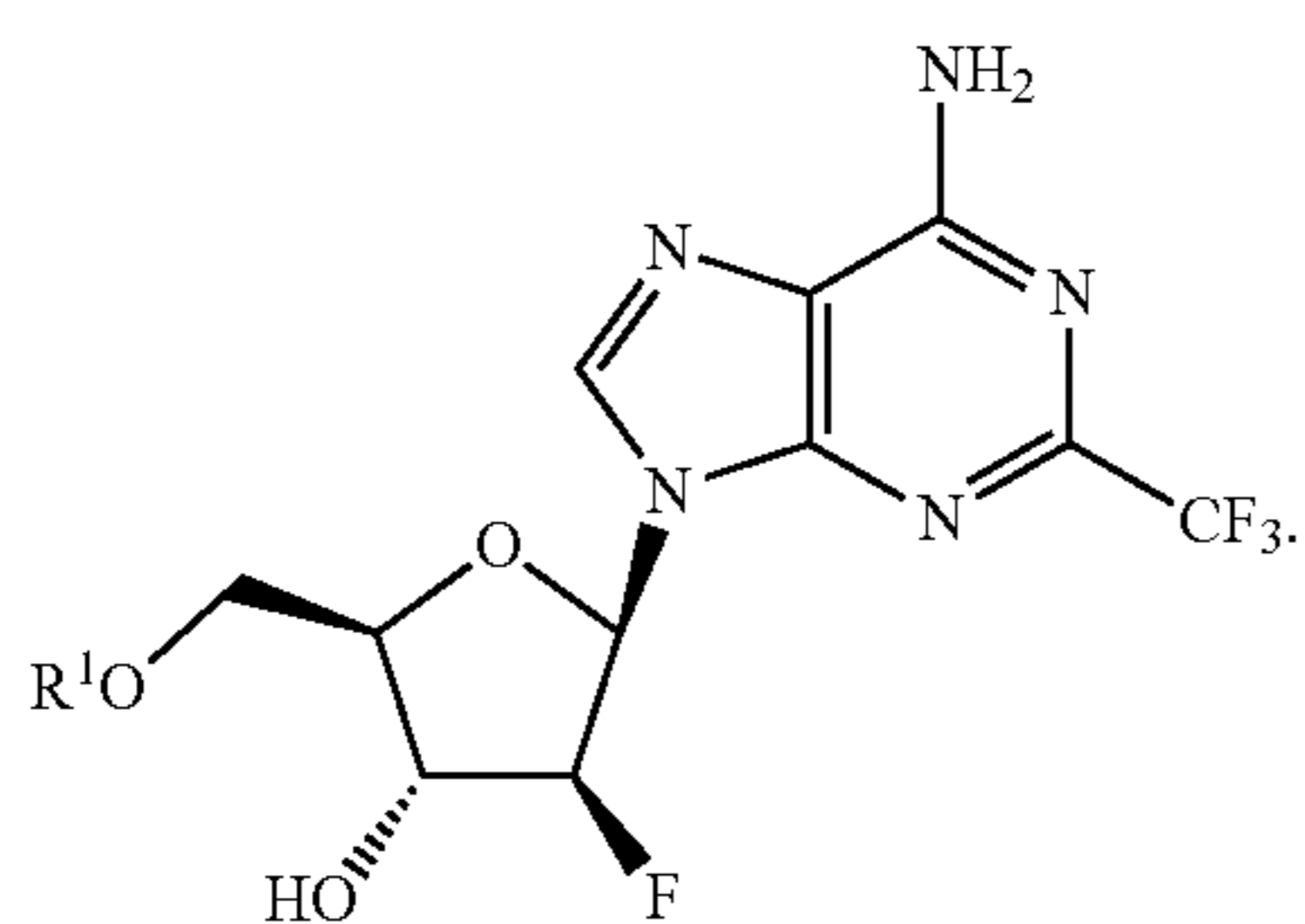
In various aspects, the compound has a structure represented by a formula:



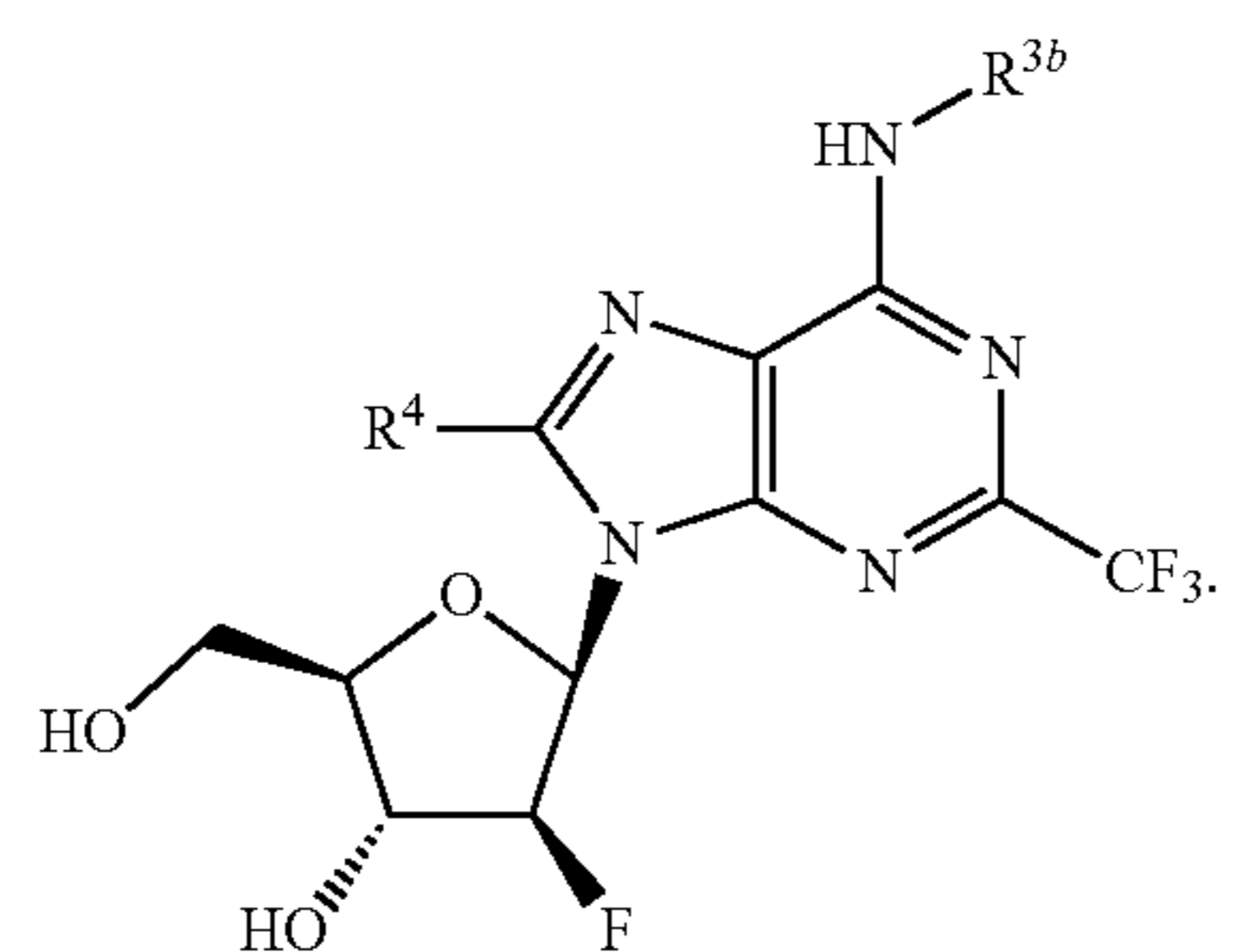
In various aspects, the compound has a structure represented by a formula:



In various aspects, the compound has a structure represented by a formula:

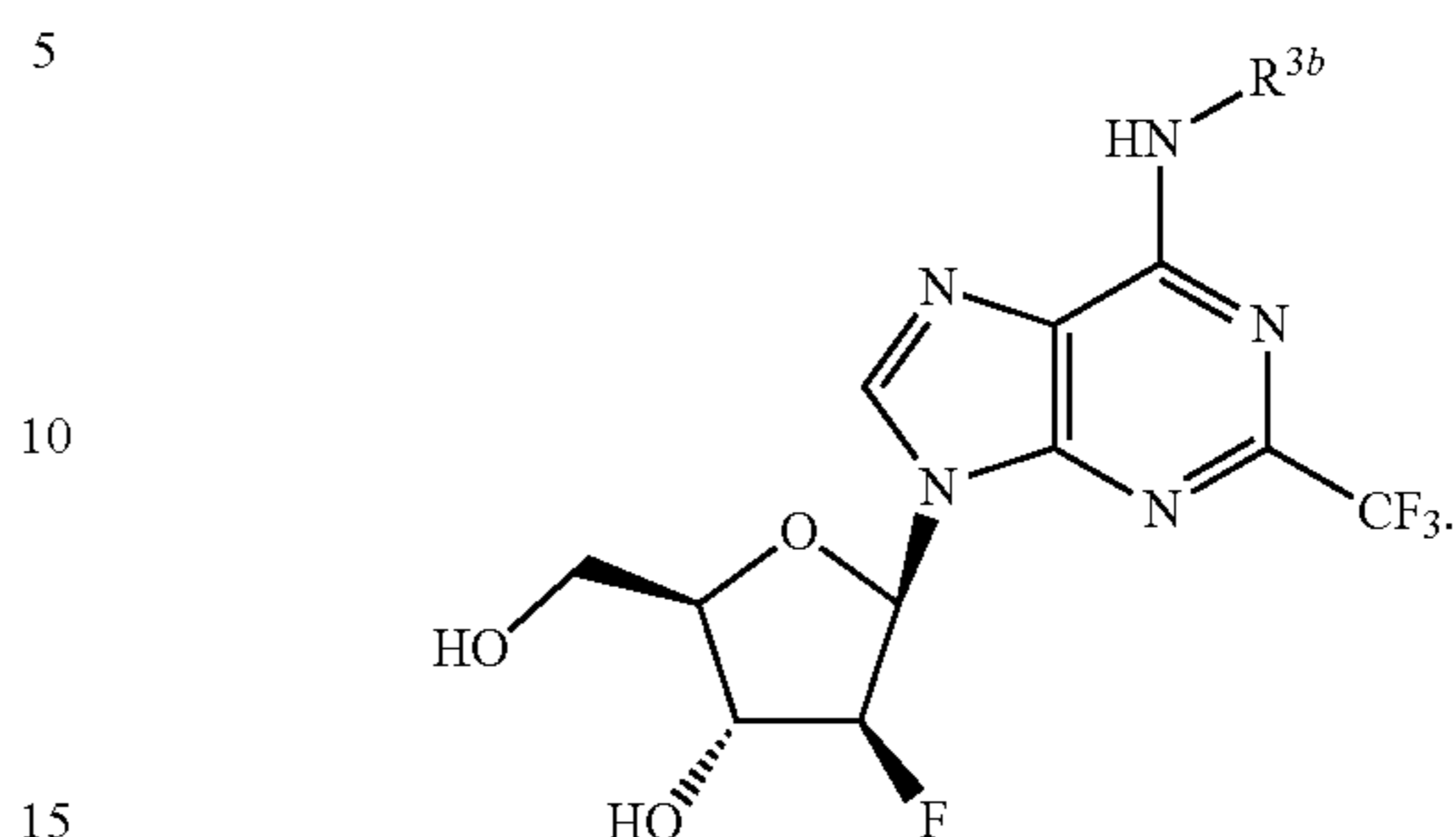


In various aspects, the compound has a structure represented by a formula:

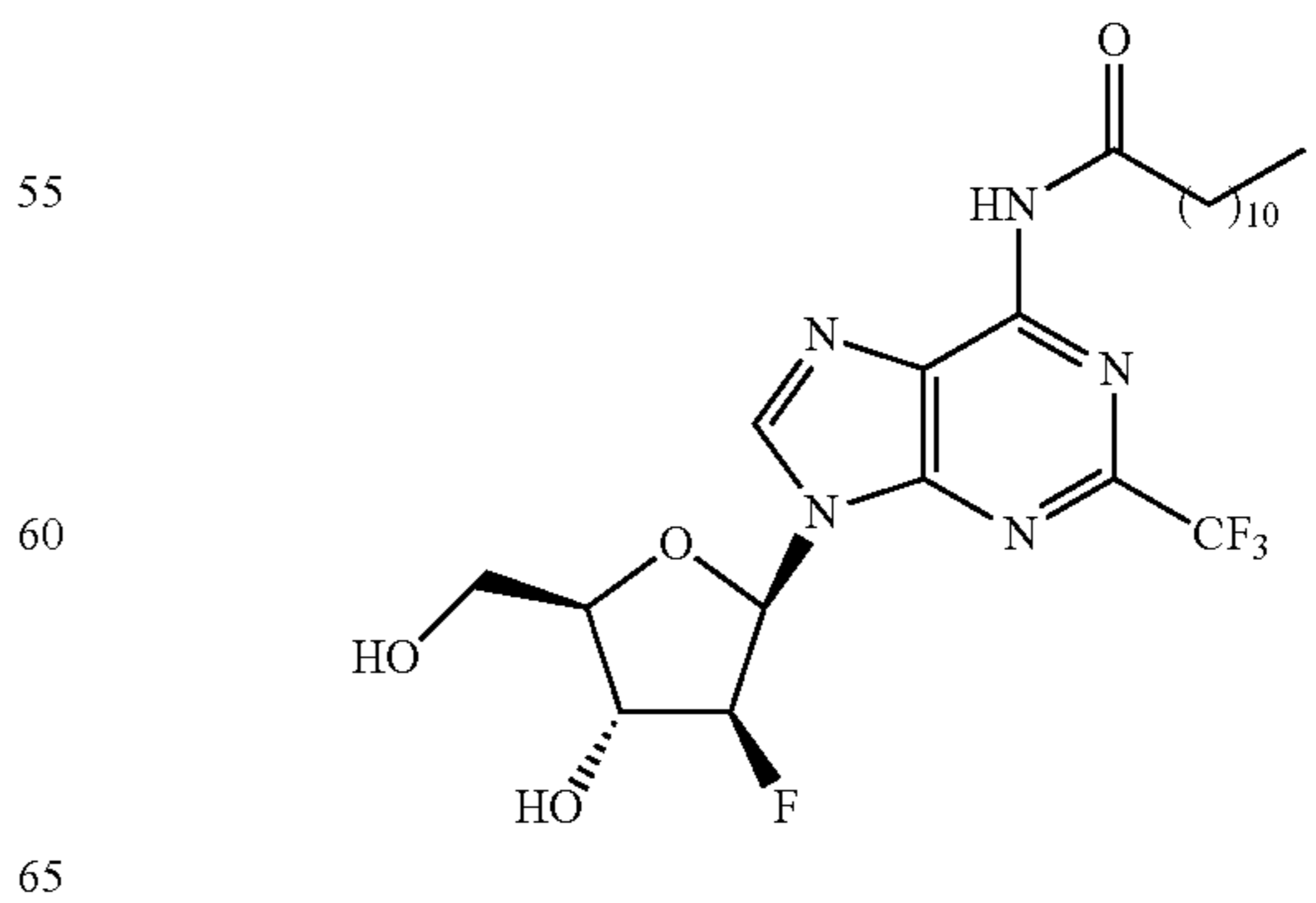
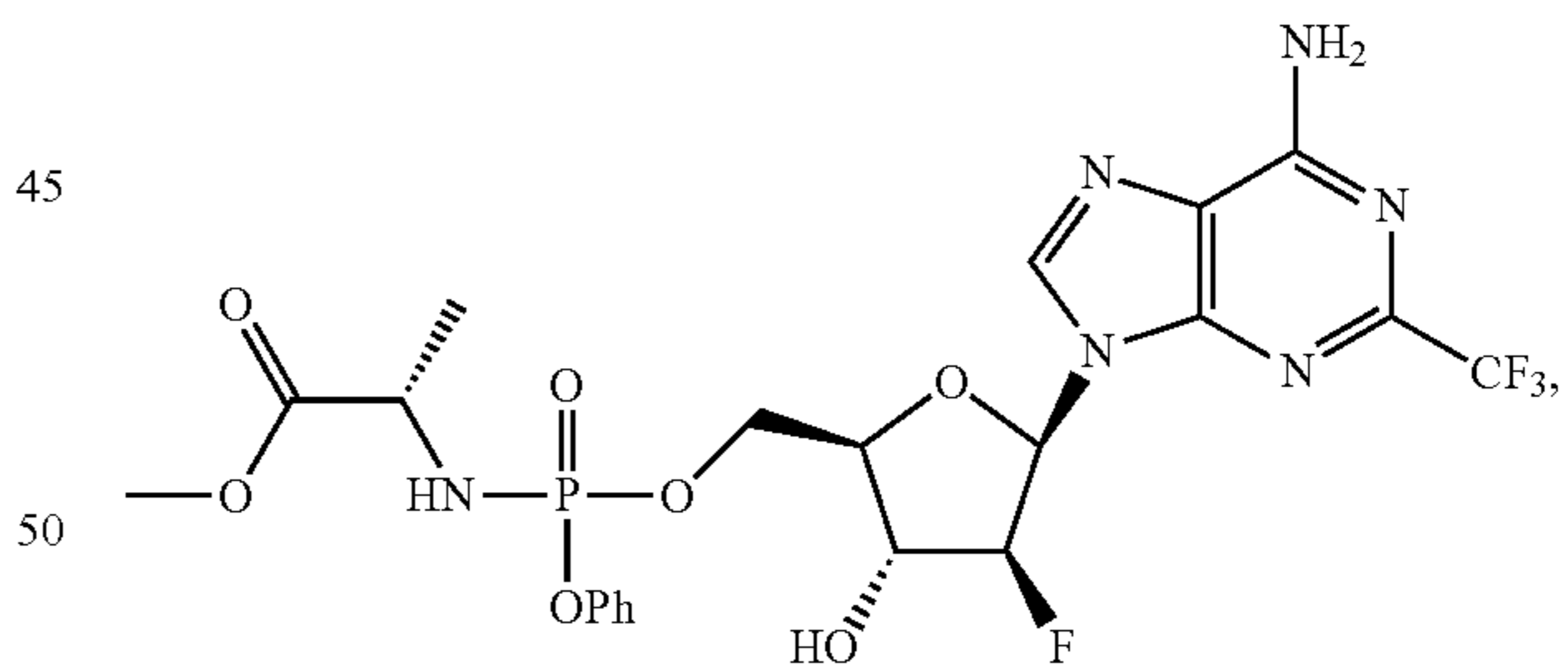
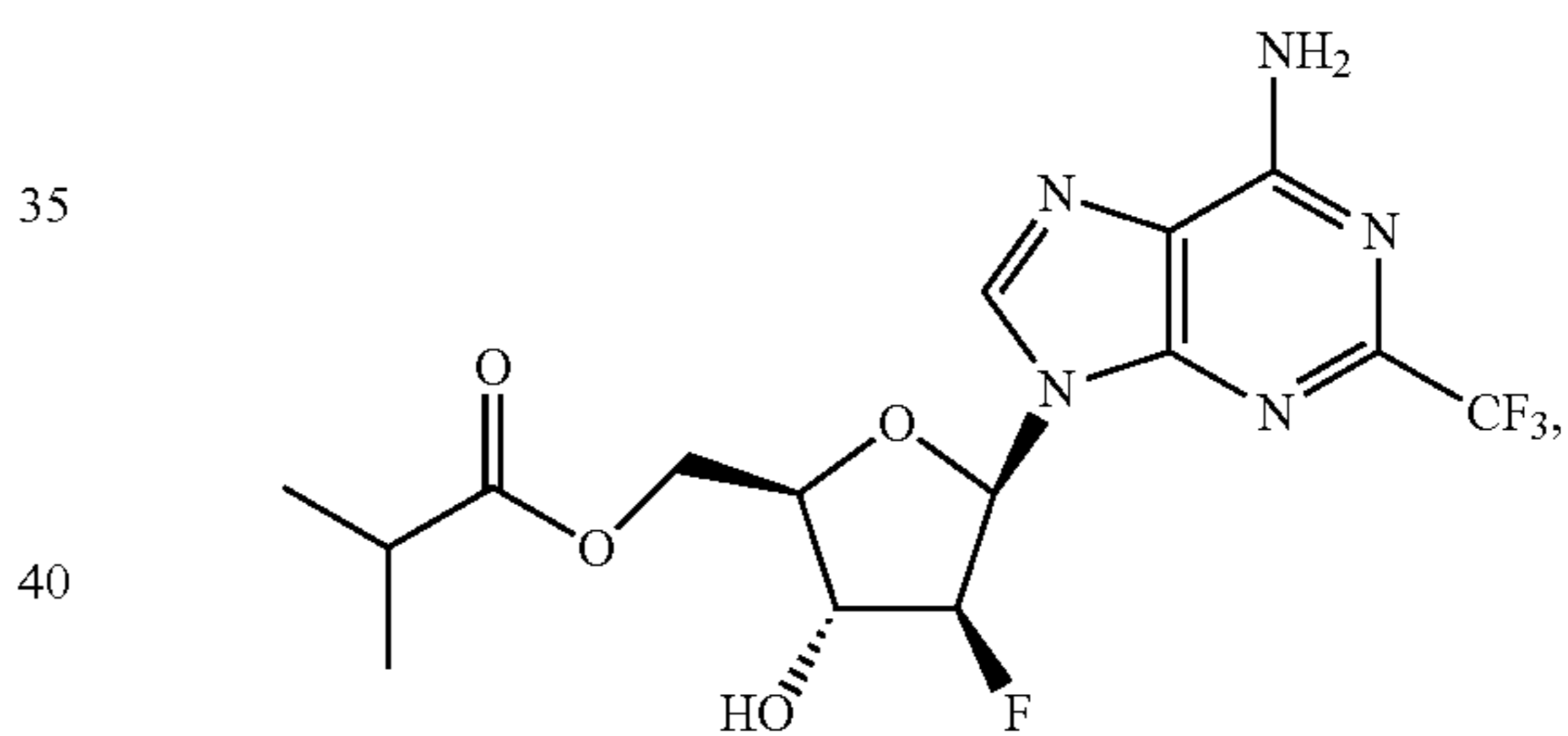
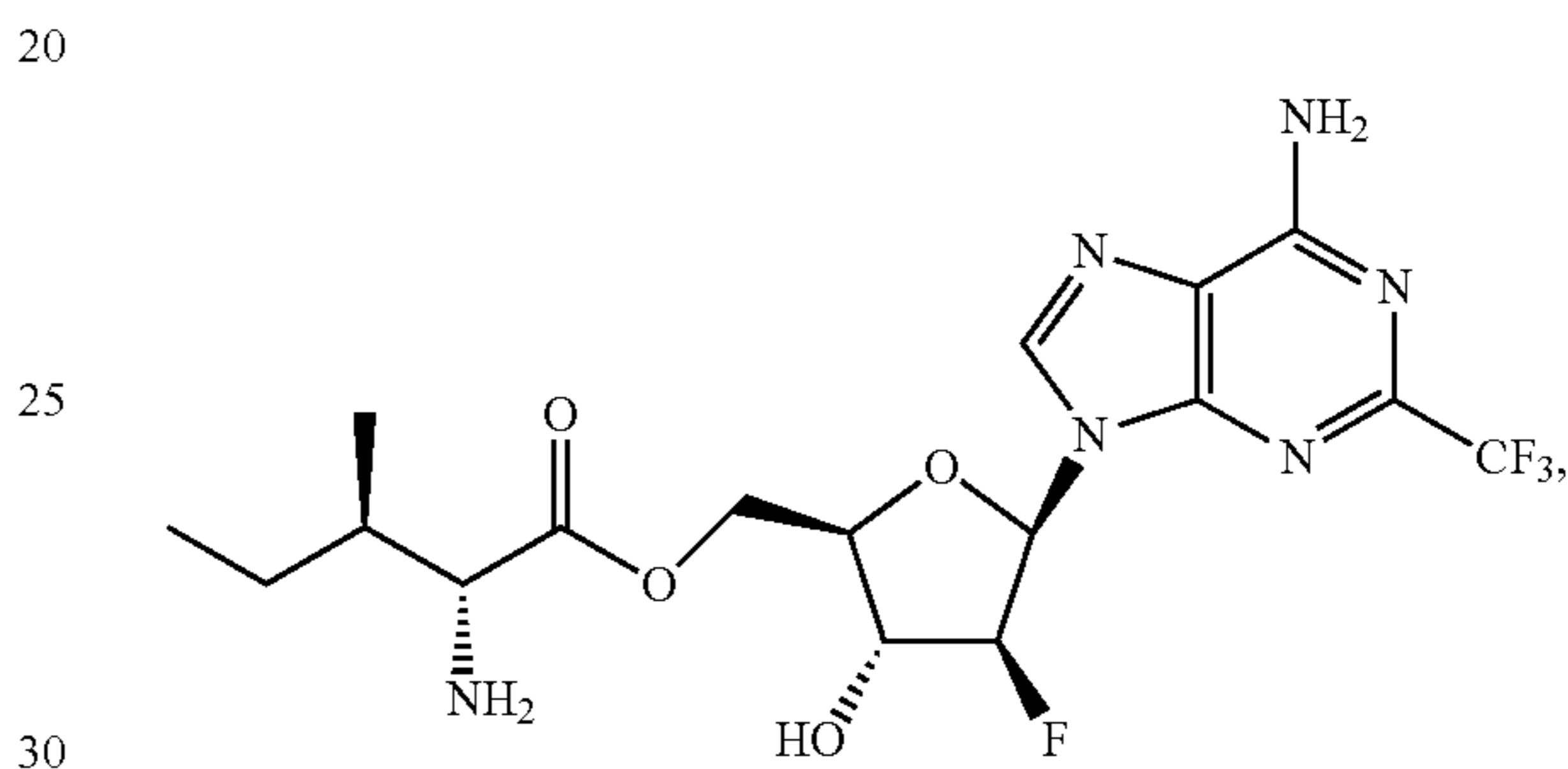


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In various aspects, the compound has a structure represented by a formula:

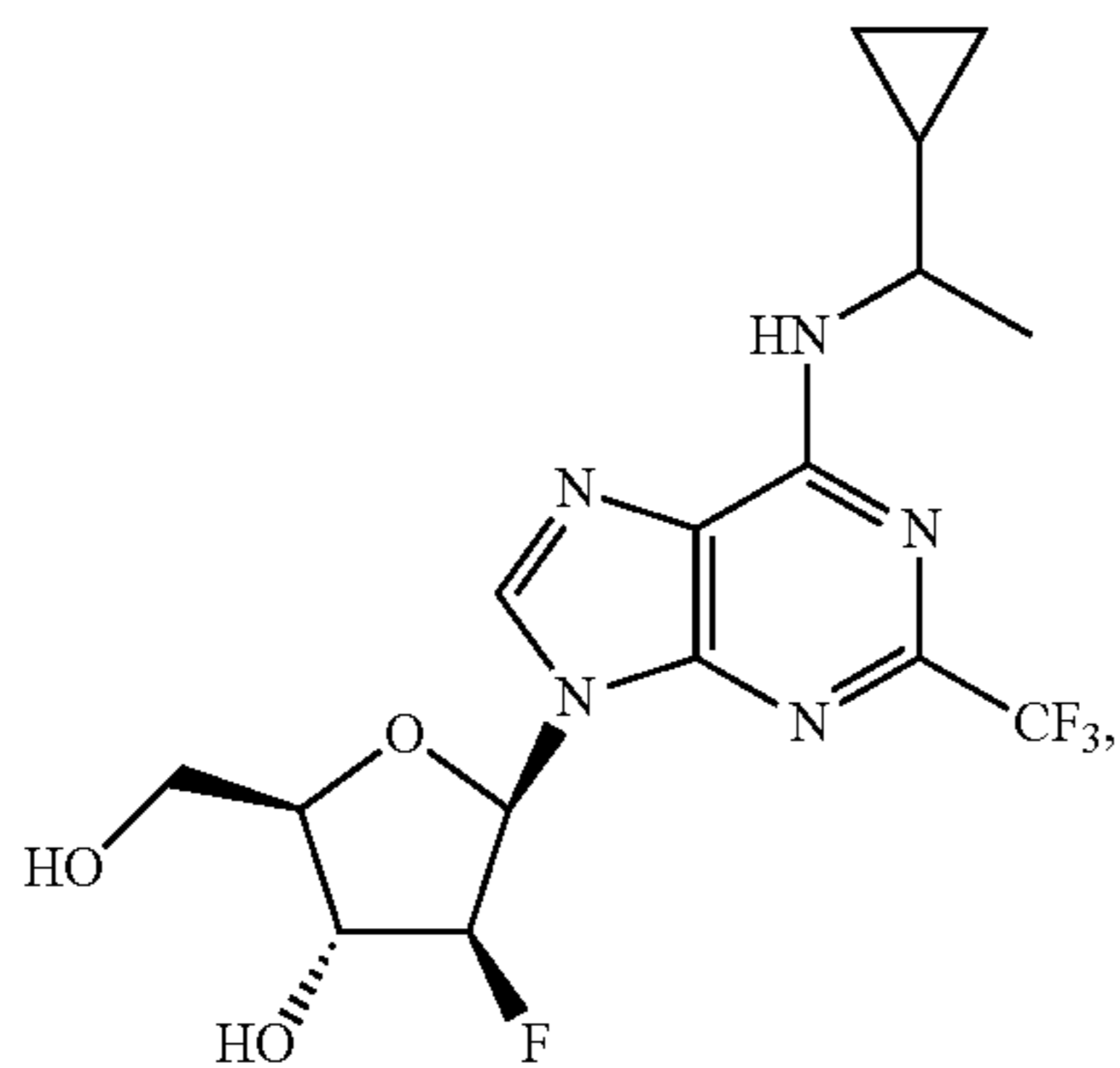
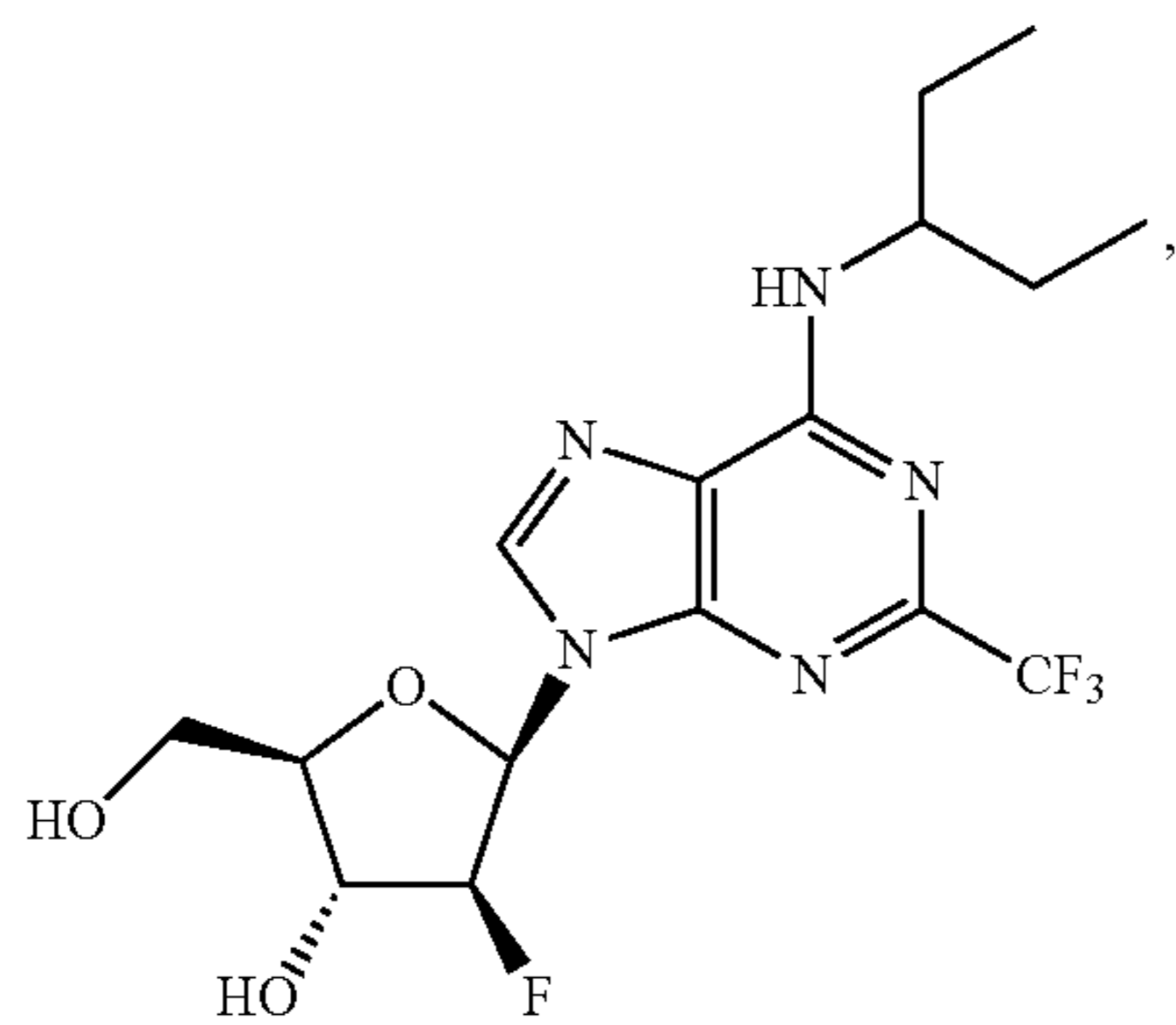
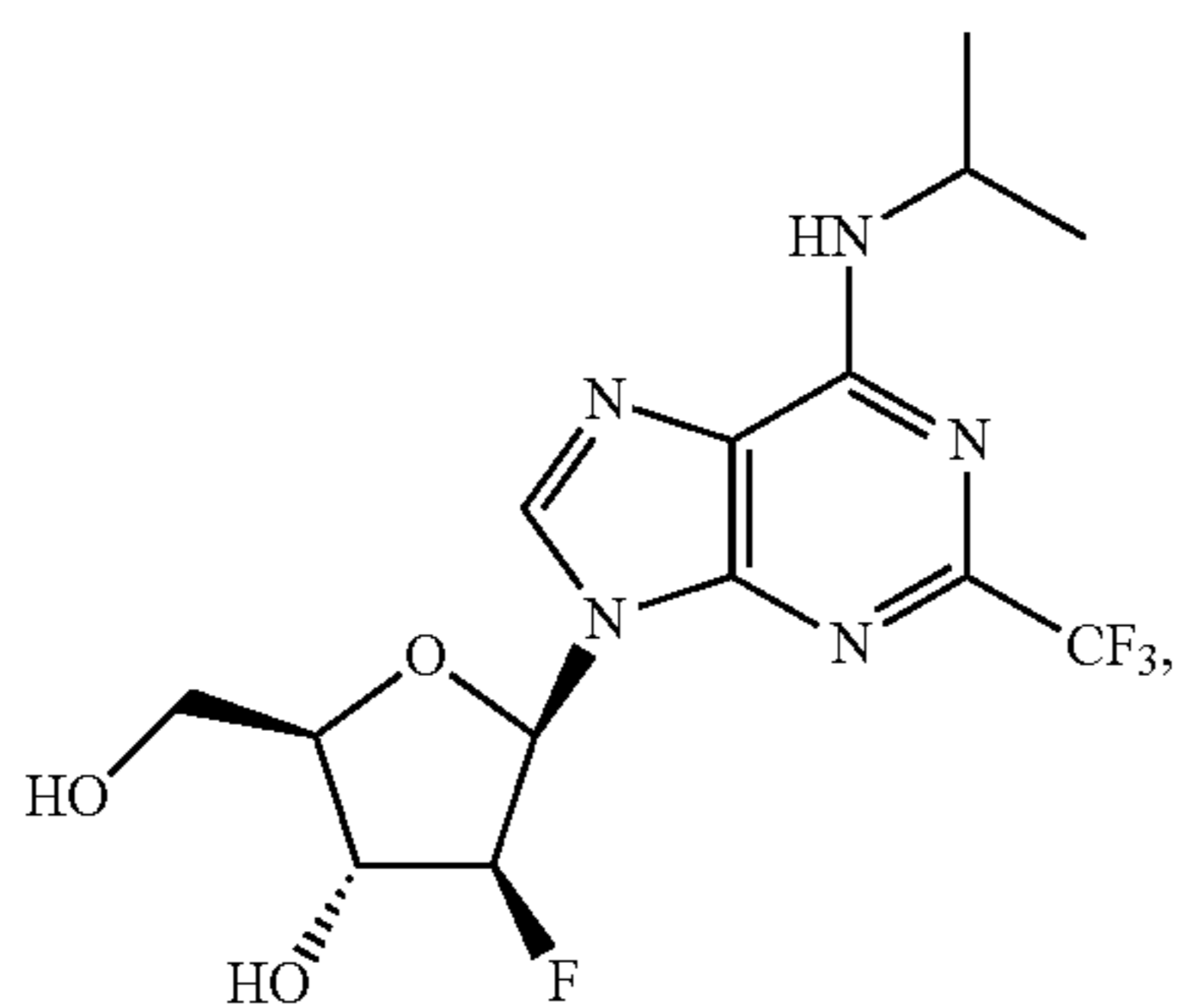
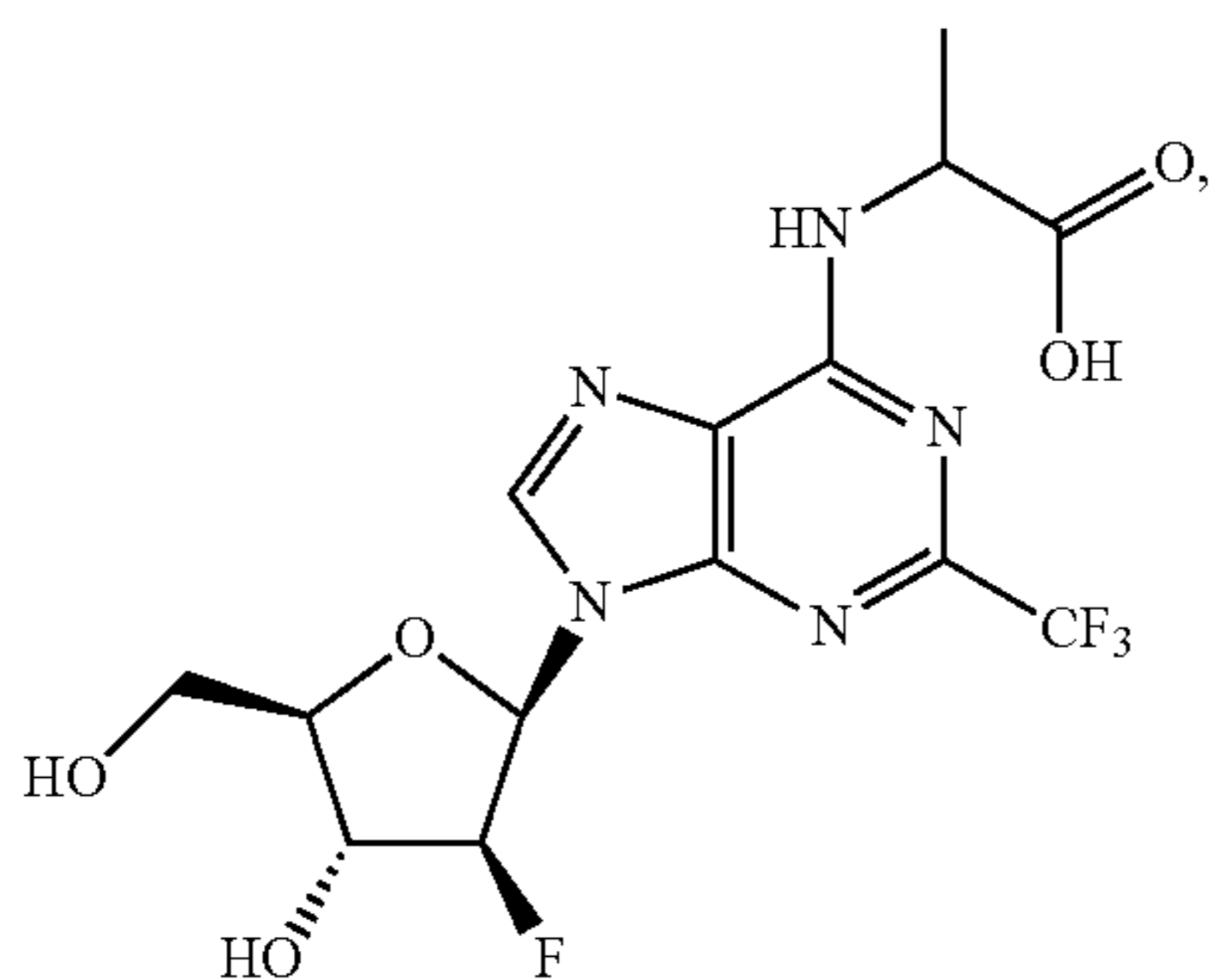
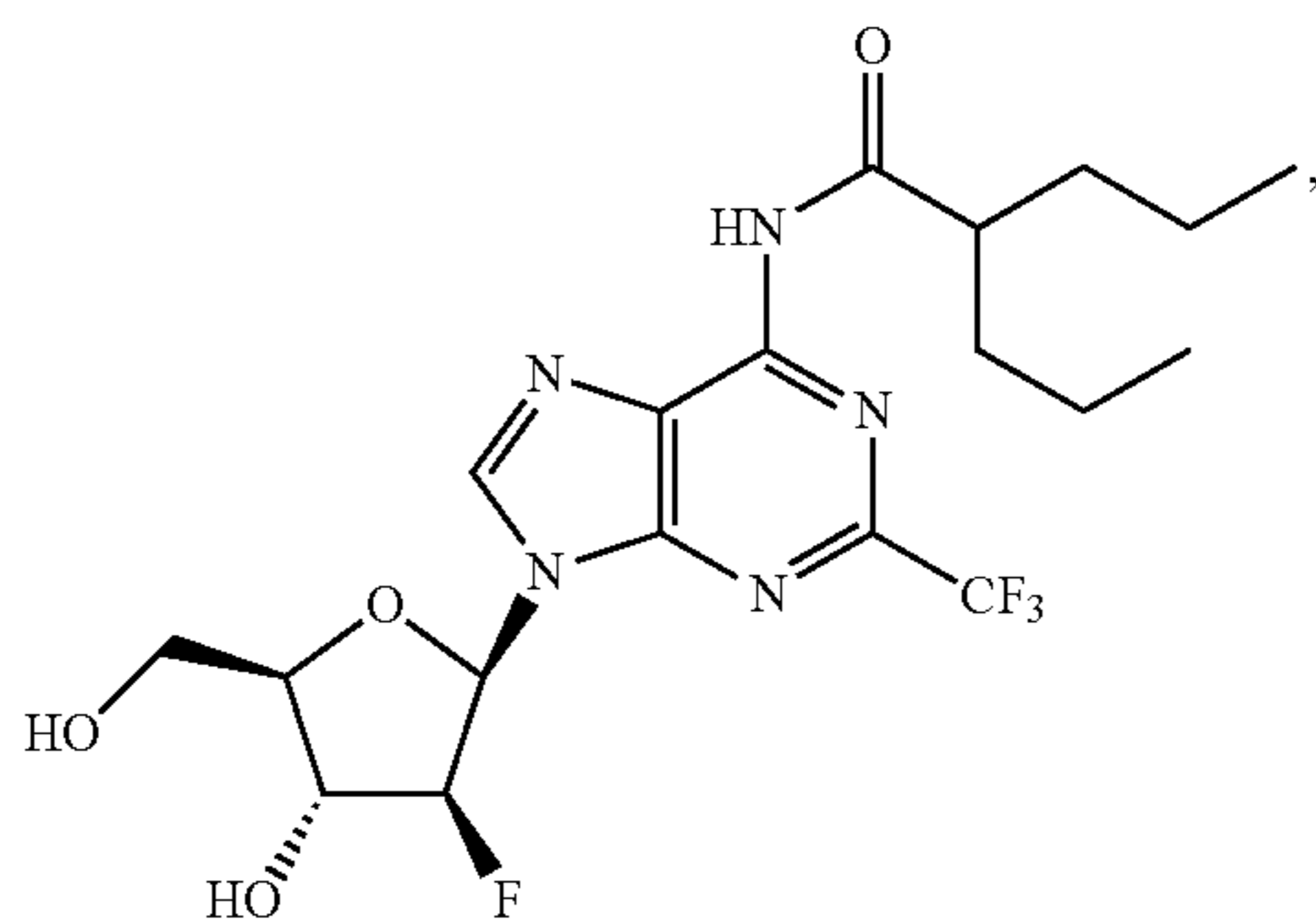


In various aspects, the compound is selected from:



47

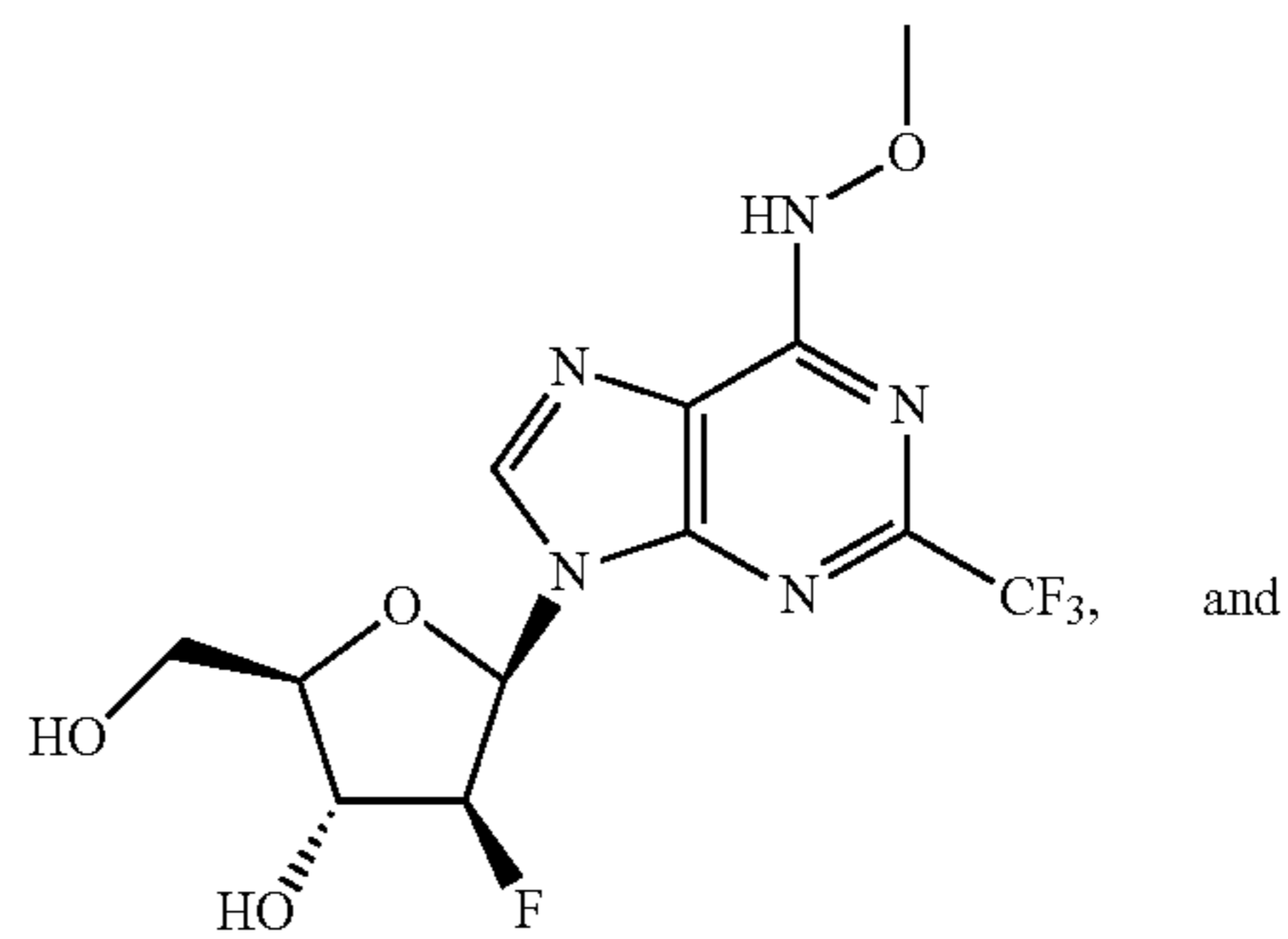
-continued



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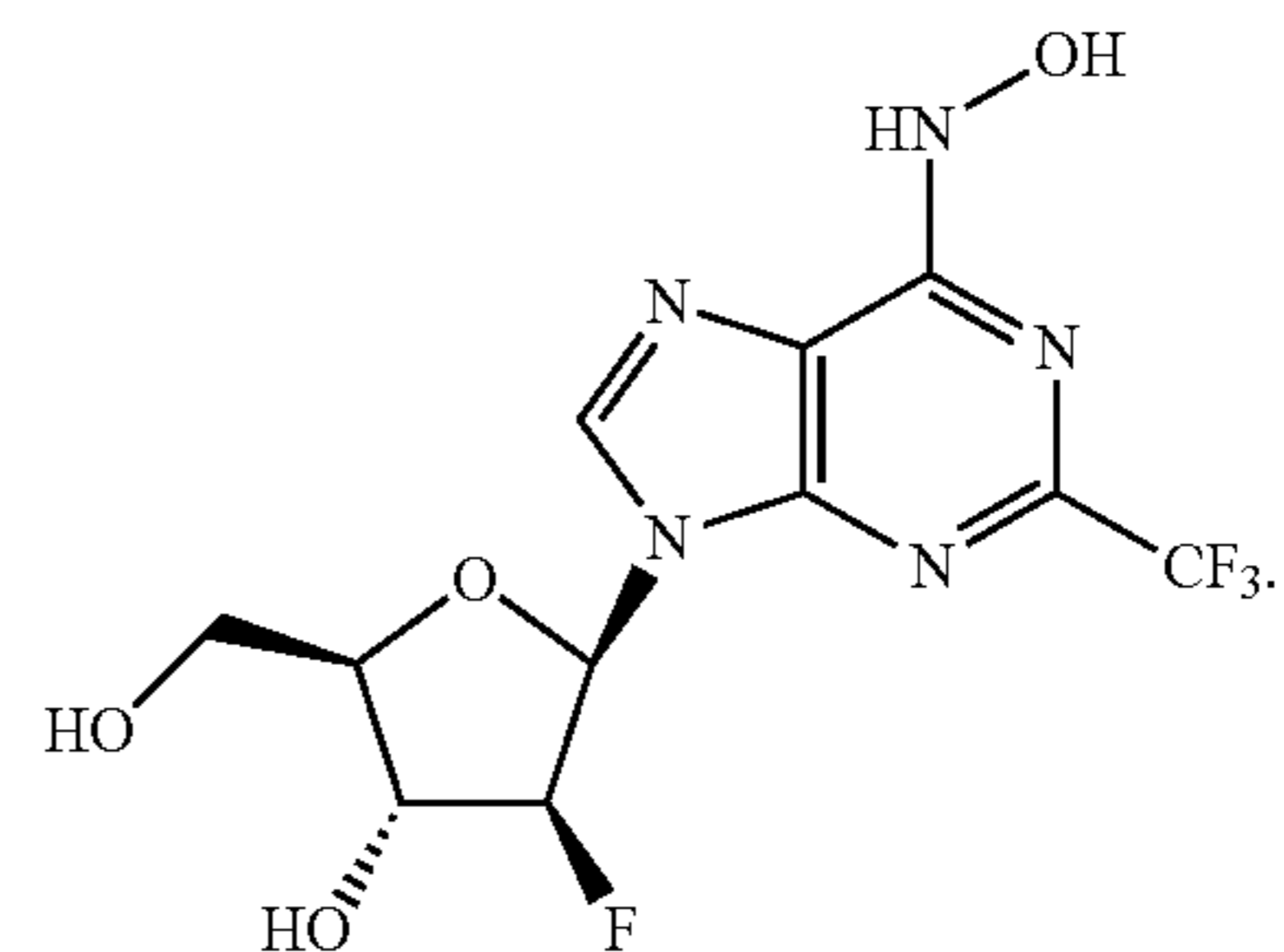


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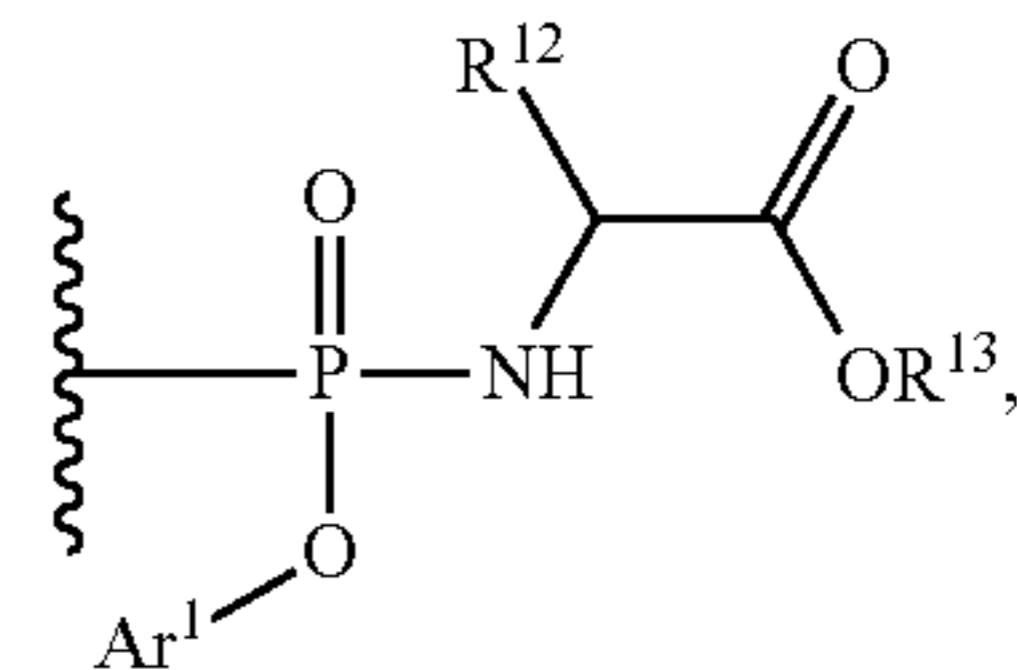
25



a. R¹ and R² Groups

In one aspect, one of R¹ and R² is hydrogen, and the other is selected from hydrogen, —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:

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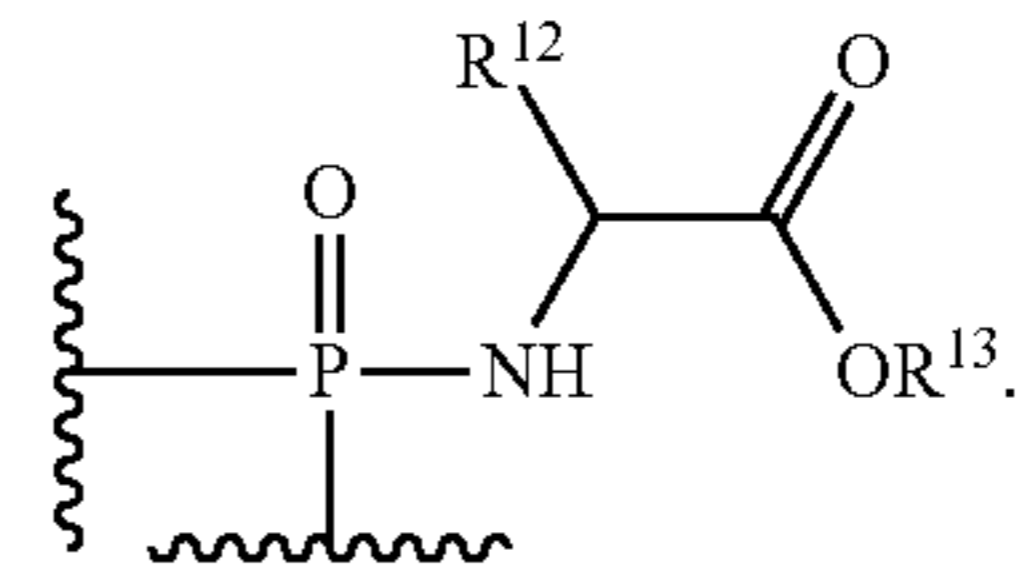


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or wherein each of R¹ and R² together comprise a structure represented by a formula:

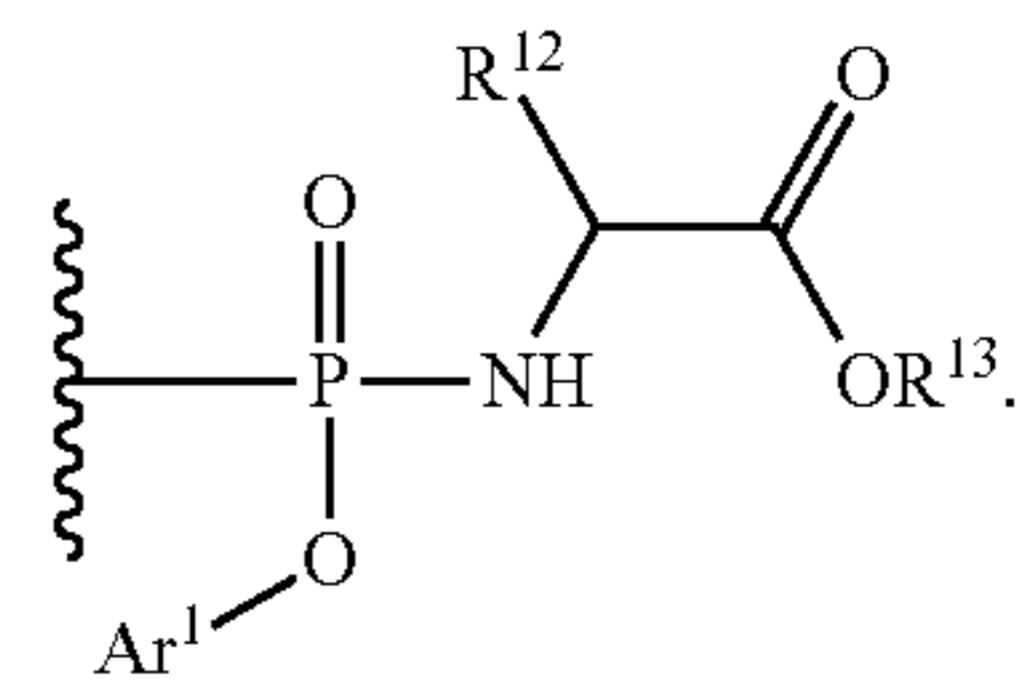
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In various aspects, one of R¹ and R² is hydrogen, and the other is selected from hydrogen, —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:

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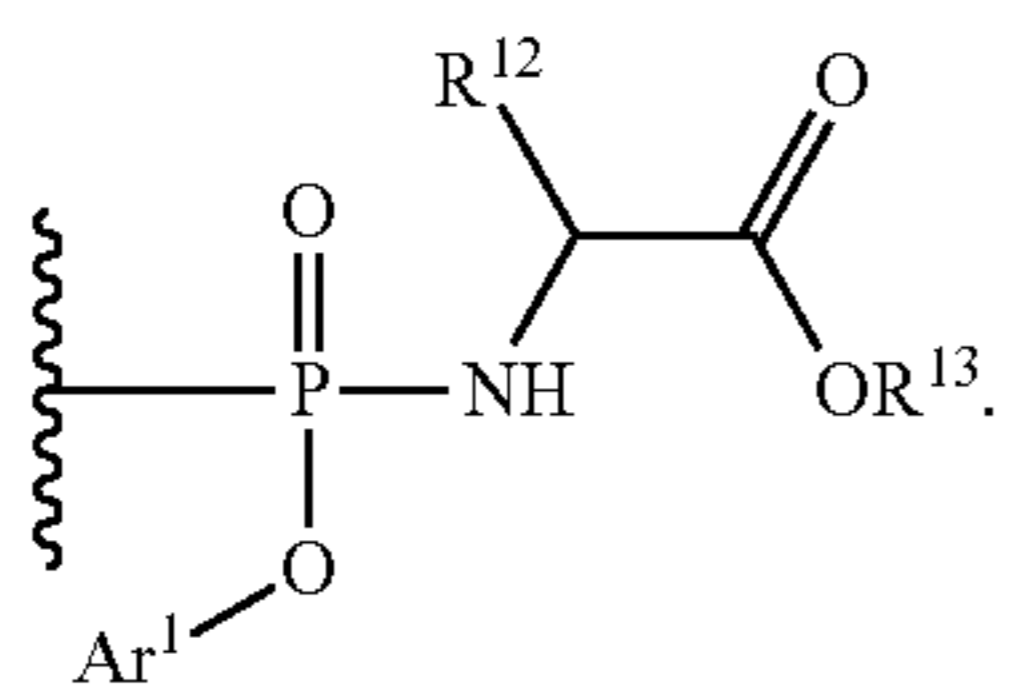


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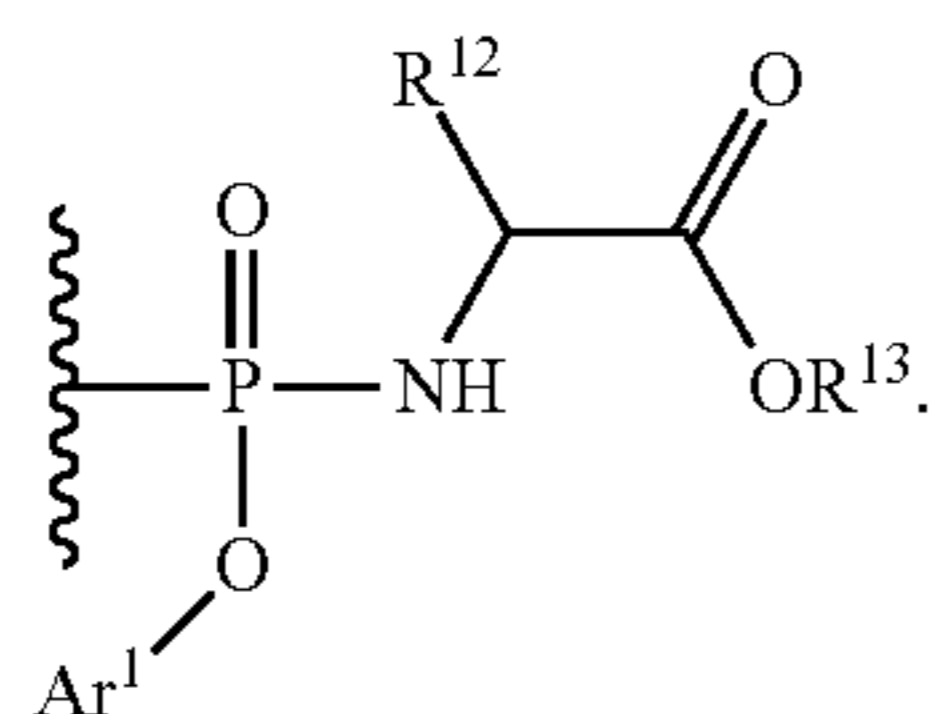
In a further aspect, one of R¹ and R² is hydrogen, and the other is selected from —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:

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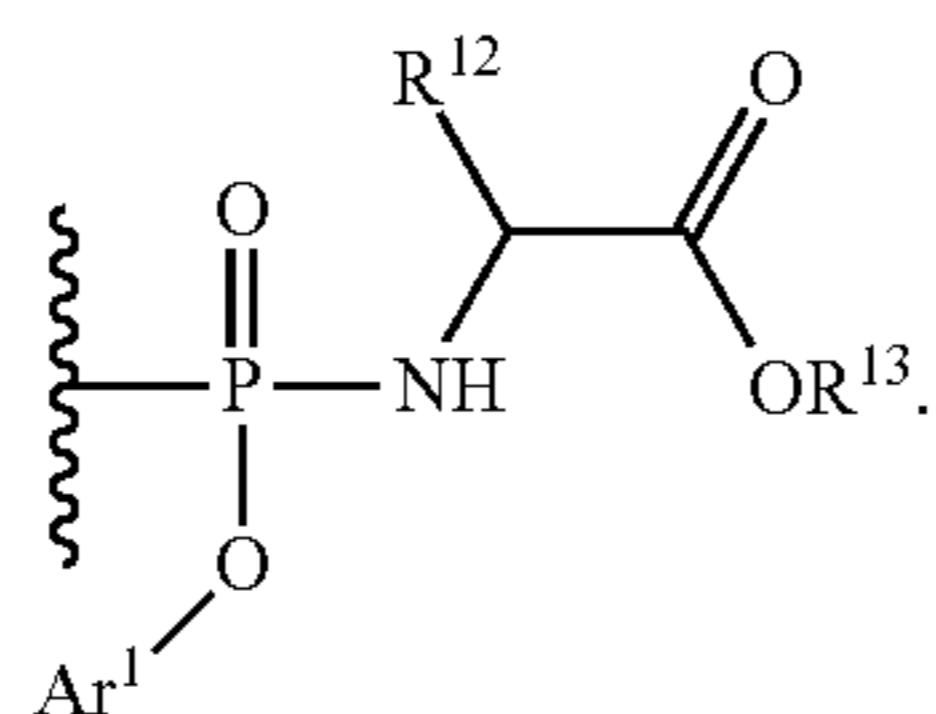
49



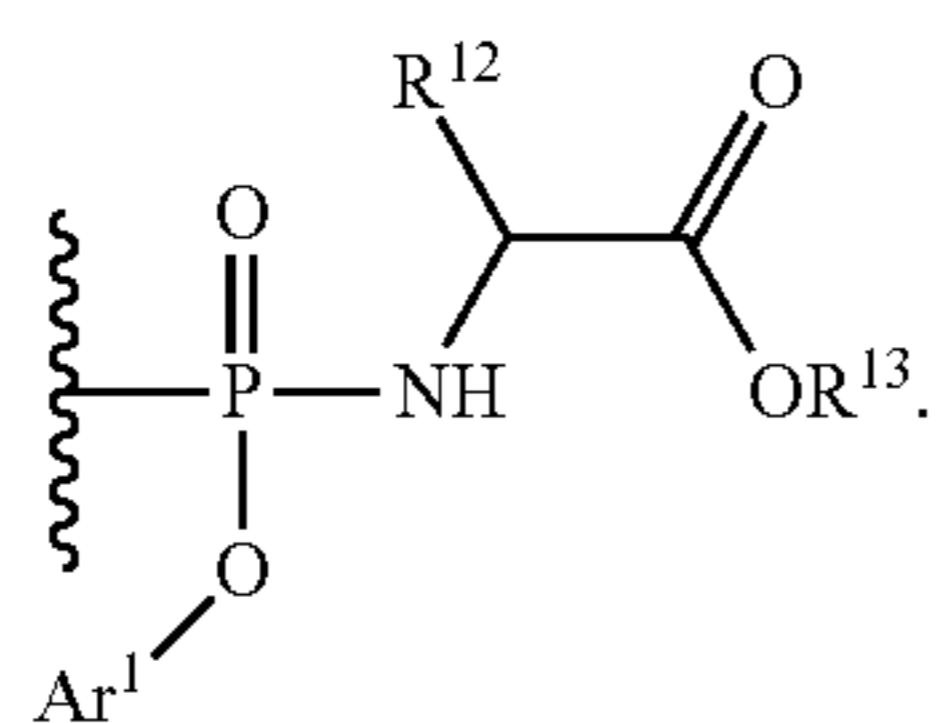
In a still further aspect, one of R¹ and R² is hydrogen, and the other is selected from —P(O)(OR¹¹)₂ and a structure represented by a formula:



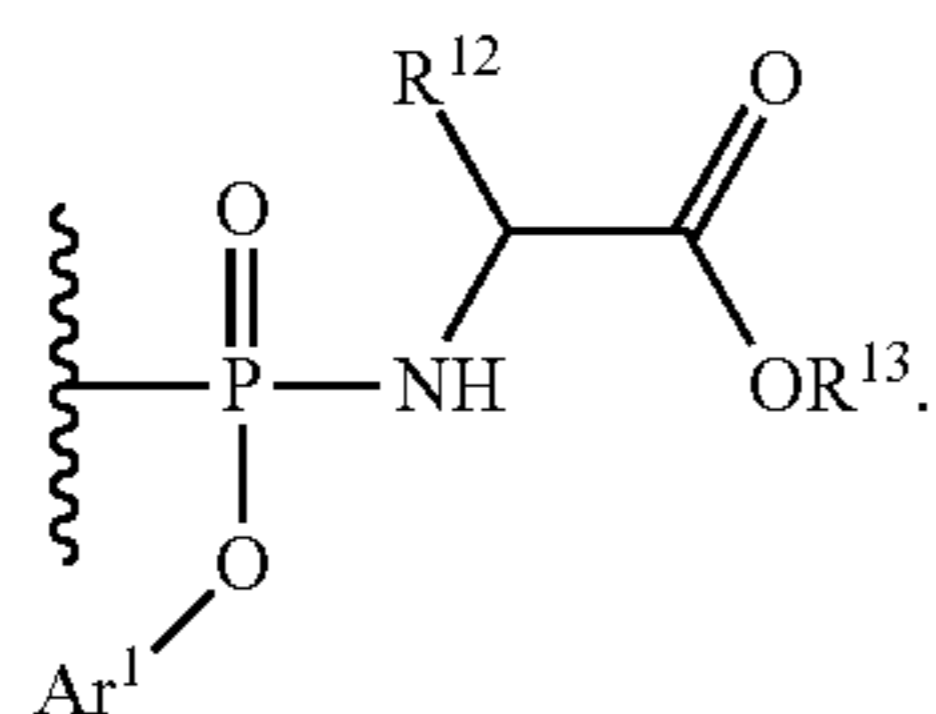
In yet a further aspect, one of R¹ and R² is hydrogen, and the other is selected from —C(O)R¹⁰ and a structure represented by a formula:



In an even further aspect, one of R¹ and R² is hydrogen, and the other is selected from —C(O)R¹⁰ and —P(O)(OR¹¹)₂. In a still further aspect, one of R¹ and R² is hydrogen, and the other is —C(O)R¹⁰. In yet a further aspect, one of R¹ and R² is hydrogen, and the other is —P(O)(OR¹¹)₂. In an even further aspect, one of R¹ and R² is hydrogen, and the other is a structure represented by a formula:

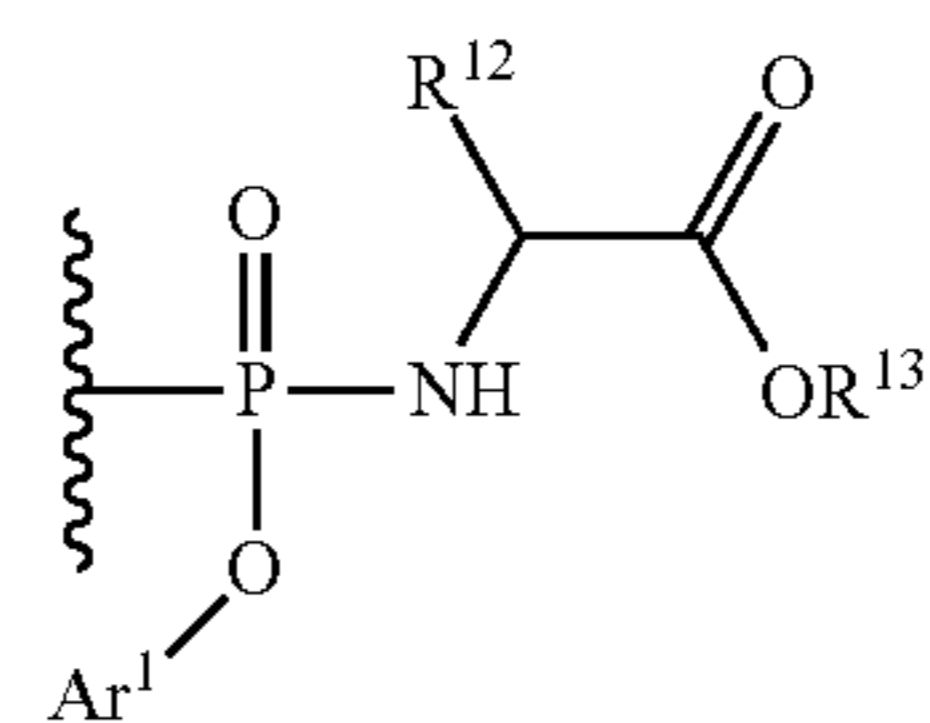


In various aspects, R¹ is hydrogen, and R² is selected from hydrogen, —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:



In a further aspect, R¹ is hydrogen, and R² is selected from —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:

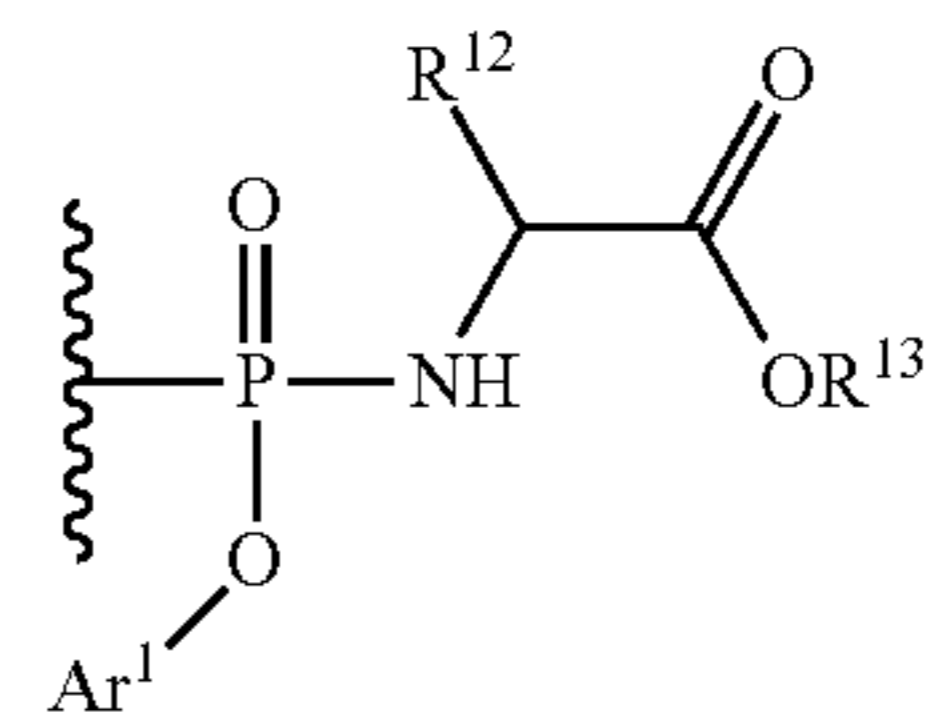
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In a still further aspect, R¹ is hydrogen, and R² is selected from —P(O)(OR¹¹)₂ and a structure represented by a formula:

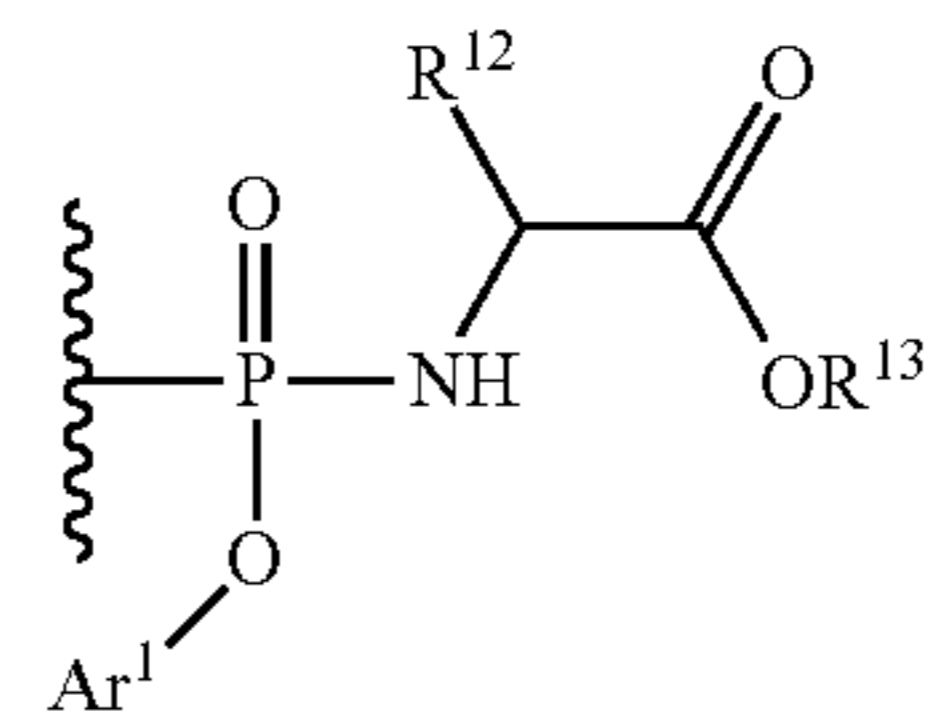
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In yet a further aspect, R¹ is hydrogen, and R² is selected from —C(O)R¹⁰ and a structure represented by a formula:

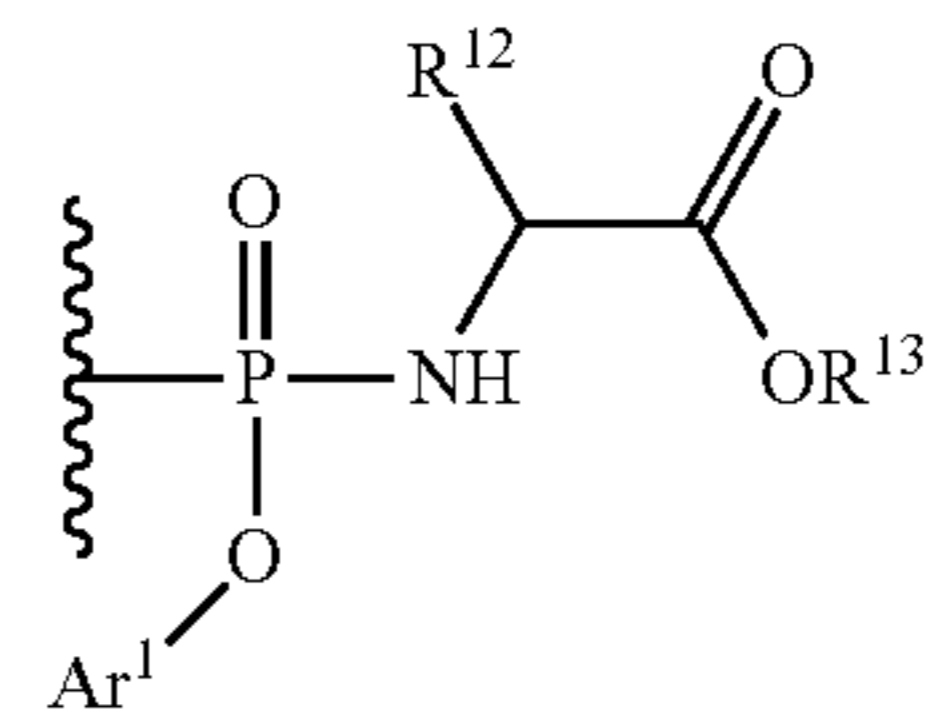
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In an even further aspect, R¹ is hydrogen, and R² is selected from —C(O)R¹⁰ and —P(O)(OR¹¹)₂. In a still further aspect, R¹ is hydrogen, and R² is —C(O)R¹⁰. In yet a further aspect, R¹ is hydrogen, and R² is —P(O)(OR¹¹)₂. In an even further aspect, R¹ is hydrogen, and R² is a structure represented by a formula:

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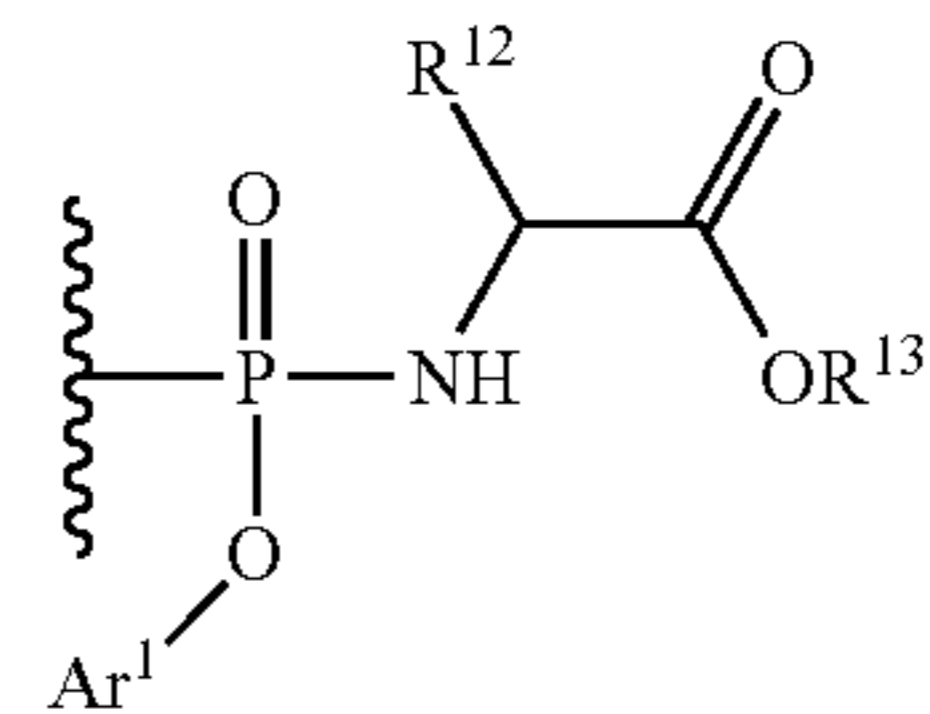


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In various aspects, R² is hydrogen, and R¹ is selected from hydrogen, —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:

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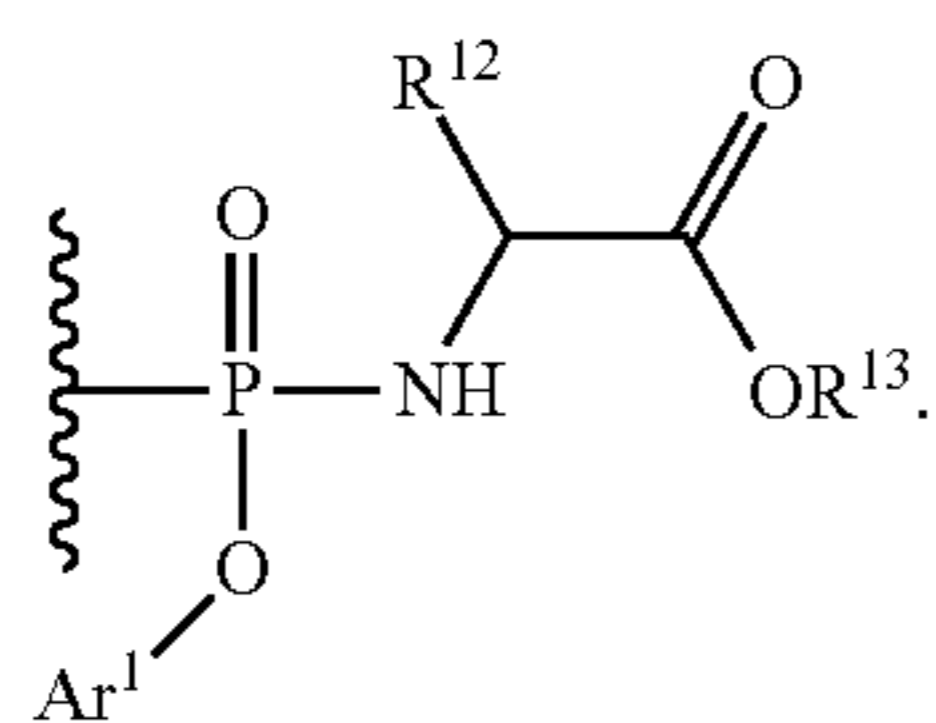


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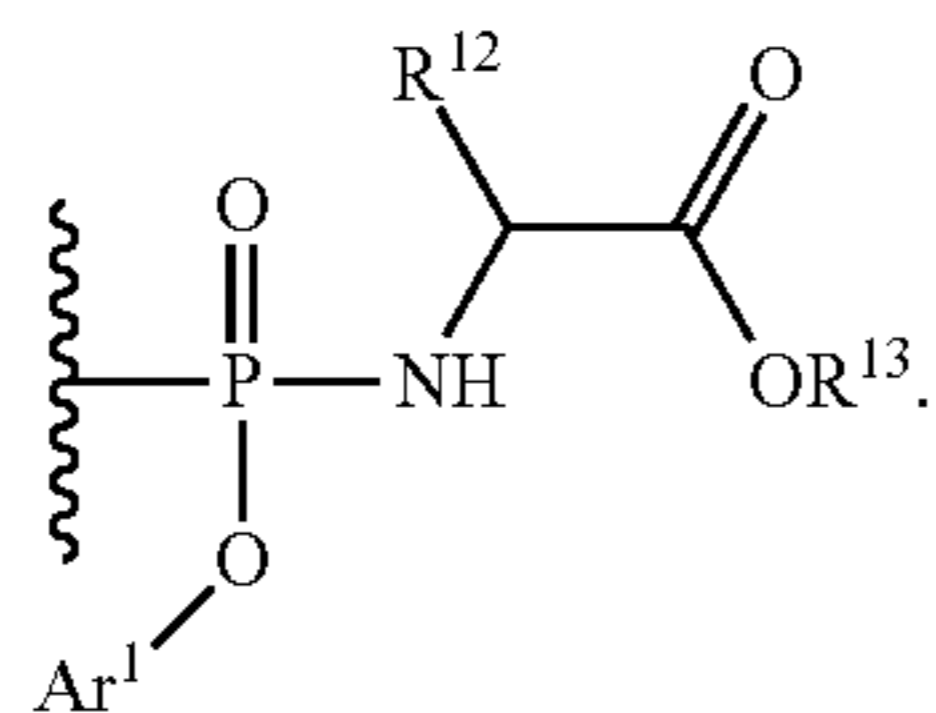
In a further aspect, R² is hydrogen, and R¹ is selected from —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:

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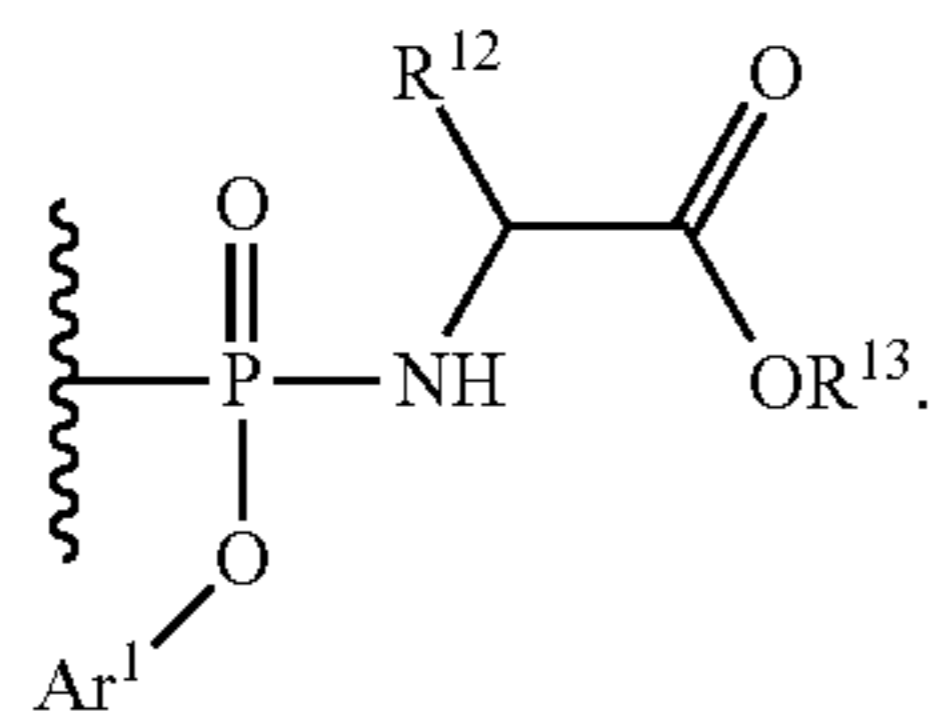
51



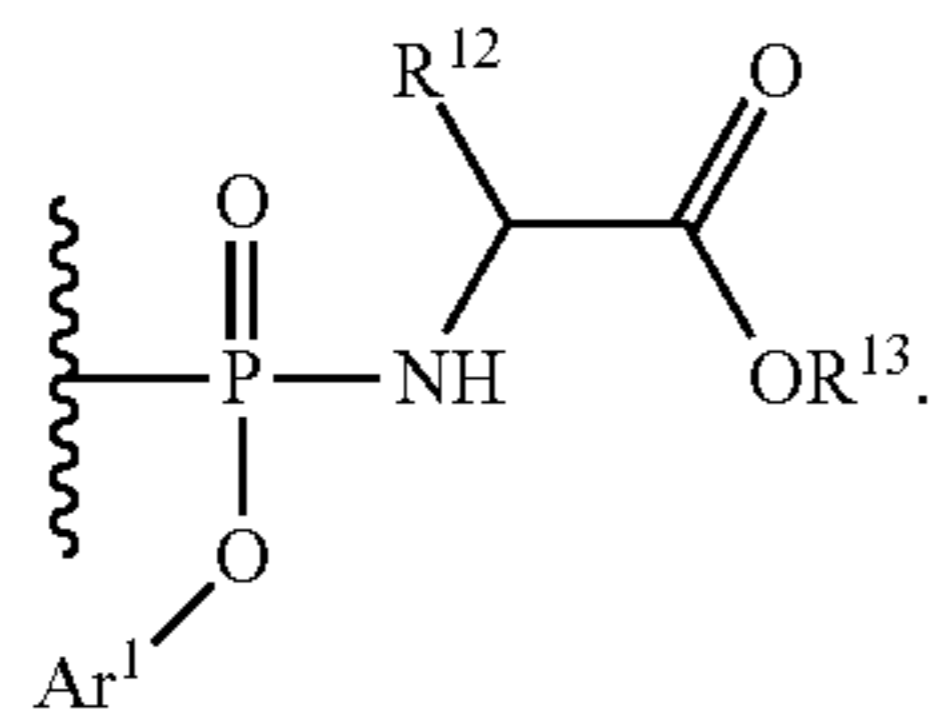
In a still further aspect, R² is hydrogen, and R¹ is selected from —P(O)(OR¹¹)₂ and a structure represented by a formula:



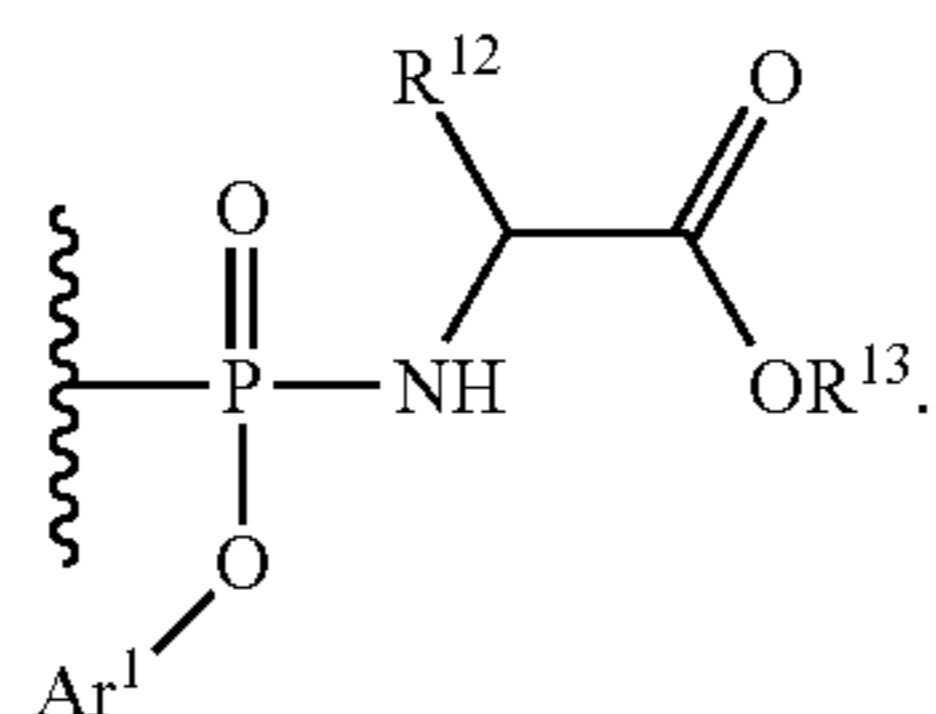
In yet a further aspect, R² is hydrogen, and R¹ is selected from —C(O)R¹⁰ and a structure represented by a formula:



In an even further aspect, R² is hydrogen, and R¹ is selected from —C(O)R¹⁰ and —P(O)(OR¹¹)₂. In a still further aspect, R² is hydrogen, and R¹ is —C(O)R¹⁰. In yet a further aspect, R² is hydrogen, and R¹ is —P(O)(OR¹¹)₂. In an even further aspect, R² is hydrogen, and R¹ is a structure represented by a formula:



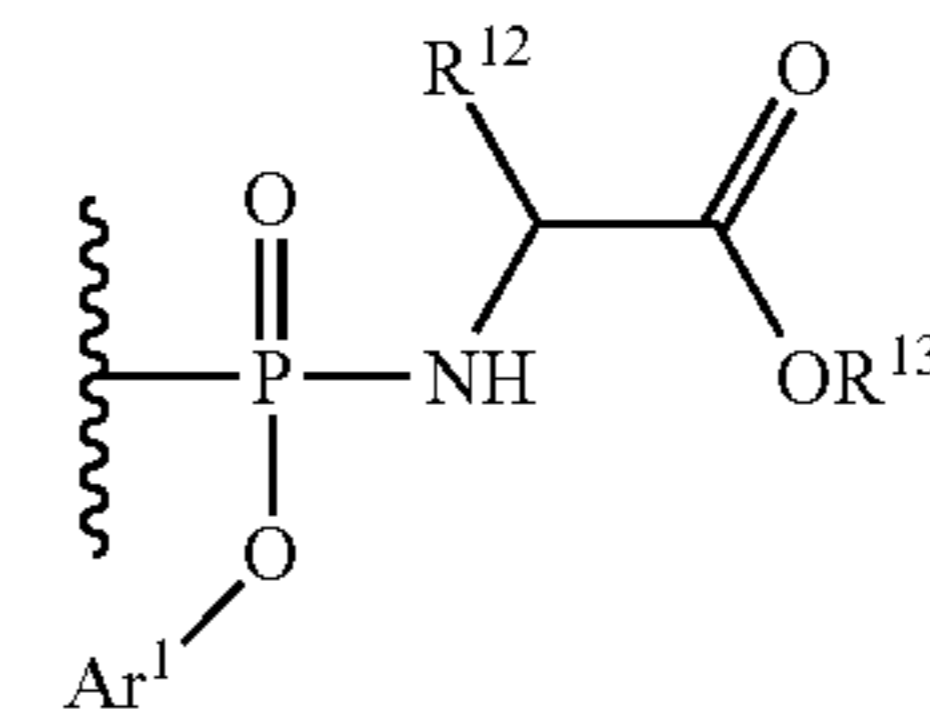
In various aspects, R² is hydrogen. In a still further aspect, R¹ is selected from —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:



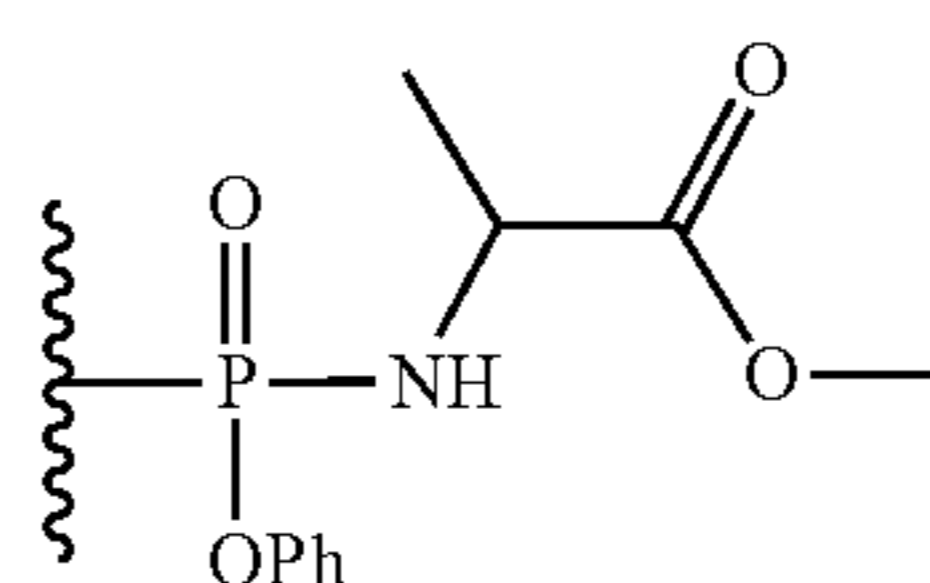
In yet a further aspect, R¹ is —C(O)R¹⁰. In a still further aspect, R¹⁰ is C1-C30 alkyl. In yet a further aspect, R¹⁰ is —CH(NH₂)R²⁰. In an even further aspect, R¹ is —C(O)CH

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(CH₃)₂. In a still further aspect, R¹ is —C(O)CH(NH₂)CH(CH₃)CH₂CH₃. In yet a further aspect, R¹ is a structure represented by a formula:

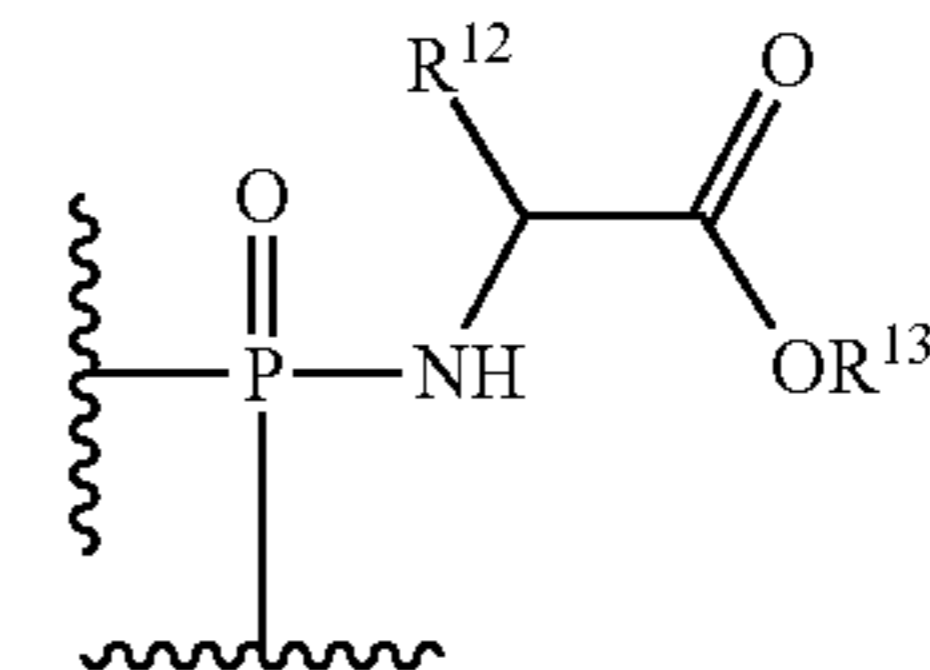


In a still further aspect, R¹ is a structure represented by a formula:



In various aspects, each of R¹ and R² is hydrogen.

In various aspects, each of R¹ and R² together comprise a structure represented by a formula:



b. R^{3a} and R^{3b} Groups

In one aspect, each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, C1-C12 alkyl, C1-C12 alkoxy, —C(O)R¹⁴, —(C1-C12 alkyl)CO₂H, and —(C1-C6 alkyl)Cy², provided that R^{3a} and R^{3b} are not simultaneously hydrogen. In a further aspect, each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, C1-C10 alkyl, C1-C10 alkoxy, —C(O)R¹⁴, —(C1-C10 alkyl)CO₂H, and —(C1-C6 alkyl)Cy². In a still further aspect, each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, C1-C8 alkyl, C1-C8 alkoxy, —C(O)R¹⁴, —(C1-C8 alkyl)CO₂H, and —(C1-C6 alkyl)Cy². In yet a further aspect, each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, C1-C4 alkyl, C1-C4 alkoxy, —C(O)R¹⁴, —(C1-C4 alkyl)CO₂H, and —(C1-C4 alkyl)Cy². In an even further aspect, each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy, n-propoxy, isopropoxy, —C(O)R¹⁴, —CH₂CO₂H, —CH₂CH₂CO₂H, —CH(CH₃)CH₂CO₂H, —CH₂CH₂CH₂CO₂H, —CH₂Cy₂, —CH₂CH₂Cy₂, —CH(CH₃)CH₂Cy₂, and —CH₂CH₂CH₂Cy₂. In a still further aspect, each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, methyl, ethyl, methoxy, ethoxy, —C(O)R¹⁴, —CH₂CO₂H, —CH₂CH₂CO₂H, —CH₂Cy₂, and —CH₂CH₂Cy₂. In yet a further aspect, each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, methyl, methoxy, —C(O)R¹⁴, —CH₂CO₂H, and —CH₂Cy₂.

In various aspects, each of R^{3a} and R^{3b} is independently selected from hydrogen, C1-C12 alkyl, and —(C1-C6 alkyl)Cy², provided that R^{3a} and R^{3b} are not simultaneously hydrogen. In a further aspect, each of R^{3a} and R^{3b} is

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is selected from —OH, methoxy, and ethoxy. In yet a further aspect, R^{3a} is hydrogen and R^{3b} is selected from —OH and methoxy.

In various aspects, R^{3a} is hydrogen and R^{3b} is C1-C12 alkyl. In a further aspect, R^{3a} is hydrogen and R^{3b} is C1-C10 alkyl. In a still further aspect, R^{3a} is hydrogen and R^{3b} is C1-C8 alkyl. In yet a further aspect, R^{3a} is hydrogen and R^{3b} is C1-C4 alkyl. In an even further aspect, R^{3a} is hydrogen and R^{3b} is selected from methyl, ethyl, n-propyl, and isopropyl. In a still further aspect, R^{3a} is hydrogen and R^{3b} is selected from methyl and ethyl.

In yet a further aspect, R^{3a} is hydrogen and R^{3b} is methyl.

In various aspects, R^{3a} is hydrogen and R^{3b} is selected from $—C(O)R^{14}$ and $—(C1-C12\text{ alkyl})CO_2H$. In a further aspect, R^{3a} is hydrogen and R^{3b} is selected from $—C(O)R^{14}$ and $—(C1-C10\text{ alkyl})CO_2H$. In a still further aspect, R^{3a} is hydrogen and R^{3b} is selected from $—C(O)R^{14}$ and $—(C1-C8\text{ alkyl})CO_2H$. In yet a further aspect, R^{3a} is hydrogen and R^{3b} is selected from $—C(O)R^{14}$ and $—(C1-C4\text{ alkyl})CO_2H$. In an even further aspect, R^{3a} is hydrogen and R^{3b} is selected from $—C(O)R^{14}$, $—CH_2CO_2H$, $—CH_2CH_2CO_2H$, $—CH(CH_3)CH_2CO_2H$, and $—CH_2CH_2CH_2CO_2H$. In a still further aspect, R^{3a} is hydrogen and R^{3b} is selected from $—C(O)R^{14}$, $—CH_2CO_2H$, and $—CH_2CH_2CO_2H$. In yet a further aspect, R^{3a} is hydrogen and R^{3b} is selected from $—C(O)R^{14}$ and $—CH_2CO_2H$.

c. R^4 Groups

In one aspect, R^4 is hydrogen or chlorine. In a further aspect, R^4 is hydrogen.

In a still further aspect, R^4 is chlorine.

d. R^{10} Groups

In one aspect, R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $—CH(NH_2)R^{20}$. In a further aspect, R^{10} , when present, is selected from C1-C15 alkyl, C2-C15 alkenyl, and $—CH(NH_2)R^{20}$. In a still further aspect, R^{10} , when present, is selected from C1-C8 alkyl, C2-C8 alkenyl, and $—CH(NH_2)R^{20}$. In yet a further aspect, R^{10} , when present, is selected from C1-C4 alkyl, C2-C4 alkenyl, and $—CH(NH_2)R^{20}$. In an even further aspect, R^{10} , when present, is selected from methyl, ethyl, isopropyl, n-propyl, ethenyl, propenyl, and $—CH(NH_2)R^{20}$. In a still further aspect, R^{10} , when present, is selected from methyl, ethyl, isopropyl, ethenyl, and $—CH(NH_2)R^{20}$. In yet a further aspect, R^{10} , when present, is selected from methyl and $—CH(NH_2)R^{20}$.

In a further aspect, R^{10} , when present, is selected from C1-C30 alkyl and C2-C30 alkenyl. In a still further aspect, R^{10} , when present, is selected from C1-C15 alkyl and C2-C15 alkenyl. In yet a further aspect, R^{10} , when present, is selected from C1-C8 alkyl and C2-C8 alkenyl. In an even further aspect, R^{10} , when present, is selected from C1-C4 alkyl and C2-C4 alkenyl. In a still further aspect, R^{10} , when present, is selected from methyl, ethyl, isopropyl, n-propyl, ethenyl, and isopropenyl. In yet a further aspect, R^{10} , when present, is selected from methyl, ethyl, and ethenyl.

In a further aspect, R^{10} , when present, is selected from C1-C30 alkyl and $—CH(NH_2)R^{20}$. In a still further aspect, R^{10} , when present, is selected from C1-C15 alkyl and $—CH(NH_2)R^{20}$. In yet a further aspect, R^{10} , when present, is selected from C1-C8 alkyl and $—CH(NH_2)R^{20}$. In an even further aspect, R^{10} , when present, is selected from C1-C4 alkyl and $—CH(NH_2)R^{20}$. In a still further aspect, R^{10} , when present, is selected from methyl, ethyl, isopropyl, n-propyl, and $—CH(NH_2)R^{20}$. In yet a further aspect, R^{10} , when present, is selected from methyl, ethyl, and $—CH(NH_2)R^{20}$. In an even further aspect, R^{10} , when present, is selected from methyl and $—CH(NH_2)R^{20}$.

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In a further aspect, R^{10} , when present, is selected from C2-C30 alkenyl and $—CH(NH_2)R^{20}$. In a still further aspect, R^{10} , when present, is selected from C2-C15 alkenyl and $—CH(NH_2)R^{20}$. In yet a further aspect, R^{10} , when present, is selected from C2-C8 alkenyl and $—CH(NH_2)R^{20}$. In an even further aspect, R^{10} , when present, is selected from C2-C4 alkenyl and $—CH(NH_2)R^{20}$. In a still further aspect, R^{10} , when present, is selected from ethenyl, propenyl, and $—CH(NH_2)R^{20}$. In yet a further aspect, R^{10} , when present, is selected from ethenyl and $—CH(NH_2)R^{20}$.

In a further aspect, R^{10} , when present, is C1-C30 alkyl. In a still further aspect, R^{10} , when present, is C1-C15 alkyl. In yet a further aspect, R^{10} , when present, is C1-C8 alkyl. In an even further aspect, R^{10} , when present, is C1-C4 alkyl. In a still further aspect, R^{10} , when present, is selected from methyl, ethyl, isopropyl, and n-propyl. In yet a further aspect, R^{10} , when present, is selected from methyl and ethyl. In an even further aspect, R^{10} , when present, is ethyl. In a still further aspect, R^{10} , when present, is methyl.

In a further aspect, R^{10} , when present, is C2-C30 alkenyl. In a still further aspect, R^{10} , when present, is C2-C15 alkenyl. In yet a further aspect, R^{10} , when present, is C2-C8 alkenyl. In an even further aspect, R^{10} , when present, is C2-C4 alkenyl. In a still further aspect, R^{10} , when present, is selected from ethenyl and propenyl. In yet a further aspect, R^{10} , when present, is propenyl. In an even further aspect, R^{10} , when present, is ethenyl.

In a further aspect, R^{10} , when present, is $—CH(NH_2)R^{20}$.

e. R^{11} Groups

In one aspect, R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $—(C1-C10\text{ alkyl})CO_2(C1-C10\text{ alkyl})$, $—(C1-C10\text{ alkyl})CO_2(C1-C10\text{ alkylthiol})$, $—(C1-C10\text{ alkyl})S—S—(C1-C10\text{ alkyl})$, and Ar^2 . In a further aspect, R^{11} , when present, is selected from hydrogen, C1-C15 alkyl, C1-C15 haloalkyl, $—(C1-C10\text{ alkyl})CO_2(C1-C10\text{ alkyl})$, $—(C1-C10\text{ alkyl})CO_2(C1-C10\text{ alkylthiol})$, $—(C1-C10\text{ alkyl})S—S—(C1-C10\text{ alkyl})$, and Ar^2 . In a still further aspect, R^{11} , when present, is selected from hydrogen, C1-C10 alkyl, C1-C10 haloalkyl, $—(C1-C10\text{ alkyl})CO_2(C1-C10\text{ alkyl})$, $—(C1-C10\text{ alkyl})CO_2(C1-C10\text{ alkylthiol})$, $—(C1-C10\text{ alkyl})S—S—(C1-C10\text{ alkyl})$, and Ar^2 . In yet a further aspect, R^{11} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 haloalkyl, $—(C1-C8\text{ alkyl})CO_2(C1-C8\text{ alkyl})$, $—(C1-C8\text{ alkyl})CO_2(C1-C8\text{ alkylthiol})$, $—(C1-C8\text{ alkyl})S—S—(C1-C8\text{ alkyl})$, and Ar^2 . In an even further aspect, R^{11} , when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 haloalkyl, $—(C1-C4\text{ alkyl})CO_2(C1-C4\text{ alkyl})$, $—(C1-C4\text{ alkyl})CO_2(C1-C4\text{ alkylthiol})$, $—(C1-C4\text{ alkyl})S—S—(C1-C4\text{ alkyl})$, and Ar^2 . In a still further aspect, R^{11} , when present, is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, $—CF_3$, $—CHF_2$, $—CH_2F$, $—CH_2CH_2F$, $—CH_2CH_2CH_2F$, $—CH(CH_3)CH_2F$, $—CCl_3$, $—CHCl_2$, $—CH_2Cl$, $—CH_2CH_2Cl$, $—CH_2CH_2CH_2Cl$, $—CH(CH_3)CH_2Cl$, $—CH_2CO_2CH_3$, $—CH_2CH_2CO_2CH_3$, $—CH_2CO_2CH_2CH_3$, $—CH_2CH_2CH_2CO_2CH_3$, $—CH(CH_3)CH_2CO_2CH_3$, $—CH_2CO_2CH_2SH$, $—CH_2CH_2CO_2CH_2SH$, $—CH_2CO_2CH_2CH_2SH$, $—CH_2CH_2CH_2CO_2CH_2SH$, $—CH(CH_3)CH_2CO_2CH_2SH$, $—CH_2—S—S—CH_3$, $—CH_2CH_2—S—S—CH_3$, $—CH_2—S—S—CH_2CH_3$, $—CH_2CH_2CH_2—S—S—CH_3$, $—CH(CH_3)CH_2—S—S—CH_3$, and Ar^2 . In an even further aspect, R^{11} , when present, is selected from hydrogen, methyl, ethyl, $—CF_3$, $—CHF_2$, $—CH_2F$, $—CH_2CH_2F$, $—CCl_3$, $—CHCl_2$, $—CH_2Cl$, $—CH_2CH_2Cl$, $—CH_2CO_2CH_3$, $—CH_2CH_2CO_2CH_3$, $—CH_2CO_2CH_2SH$, $—CH_2CH_2CO_2CH_2SH$, $—CH_2—$

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S—S—CH₃, —CH₂CH₂—S—S—CH₃, —CH₂—S—S—CH₂CH₃, and Ar². In a still further aspect, R¹¹, when present, is selected from hydrogen, methyl, —CF₃, —CHF₂, —CH₂F, —CCl₃, —CHCl₂, —CH₂Cl, —CH₂CO₂CH₃, —CH₂CO₂CH₂SH, —CH₂—S—S—CH₃, and Ar².

In various aspects, R¹¹, when present, is hydrogen.

In various aspects, R¹¹, when present, is selected from hydrogen, C1-C10 alkyl, C1-C10 haloalkyl, and Ar². In a further aspect, R¹¹, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 haloalkyl, and Ar². In a still further aspect, R¹¹, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 haloalkyl, and Ar². In yet a further aspect, R¹¹, when present, is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, —CF₃, —CHF₂, —CH₂F, —CH₂CH₂F, —CH₂CH₂CH₂F, —CH(CH₃)CH₂F, —CCl₃, —CHCl₂, —CH₂Cl, —CH₂CH₂Cl, —CH₂CH₂CH₂Cl, —CH(CH₃)CH₂Cl, and Ar². In an even further aspect, R¹¹, when present, is selected from hydrogen, methyl, ethyl, —CF₃, —CHF₂, —CH₂F, —CH₂CH₂F, —CCl₃, —CHCl₂, —CH₂Cl, —CH₂CH₂Cl, and Ar². In a still further aspect, R¹¹, when present, is selected from hydrogen, methyl, —CF₃, —CHF₂, —CH₂F, —CCl₃, —CHCl₂, —CH₂Cl, and Ar².

In various aspects, R¹¹, when present, is selected from hydrogen, C1-C10 alkyl, and C1-C10 haloalkyl. In a further aspect, R¹¹, when present, is selected from hydrogen, C1-C8 alkyl, and C1-C8 haloalkyl. In a still further aspect, R¹¹, when present, is selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl. In yet a further aspect, R¹¹, when present, is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, —CF₃, —CHF₂, —CH₂F, —CH₂CH₂F, —CH₂CH₂CH₂F, —CH(CH₃)CH₂F, —CCl₃, —CHCl₂, —CH₂Cl, —CH₂CH₂Cl, —CH₂CH₂CH₂Cl, and —CH(CH₃)CH₂Cl. In an even further aspect, R¹¹, when present, is selected from hydrogen, methyl, ethyl, —CF₃, —CHF₂, —CH₂F, —CH₂CH₂F, —CCl₃, —CHCl₂, —CH₂Cl, and —CH₂CH₂Cl. In a still further aspect, R¹¹, when present, is selected from hydrogen, methyl, —CF₃, —CHF₂, —CH₂F, —CCl₃, —CHCl₂, and —CH₂Cl.

In various aspects, R¹¹, when present, is selected from hydrogen and C1-C10 alkyl. In a further aspect, R¹¹, when present, is selected from hydrogen and C1-C8 alkyl. In a still further aspect, R¹¹, when present, is selected from hydrogen and C1-C4 alkyl. In yet a further aspect, R¹¹, when present, is selected from hydrogen, methyl, ethyl, n-propyl, and isopropyl. In an even further aspect, R¹¹, when present, is selected from hydrogen, methyl, and ethyl. In a still further aspect, R¹¹, when present, is selected from hydrogen and methyl.

In various aspects, R¹¹, when present, is C1-C10 haloalkyl. In a further aspect, R¹¹, when present, is C1-C8 haloalkyl. In a still further aspect, R¹¹, when present, is C1-C4 haloalkyl. In yet a further aspect, R¹¹, when present, is selected from —CF₃, —CHF₂, —CH₂F, —CH₂CH₂F, —CH₂CH₂CH₂F, —CH(CH₃)CH₂F, —CCl₃, —CHCl₂, —CH₂Cl, —CH₂CH₂Cl, —CH₂CH₂CH₂Cl, and —CH(CH₃)CH₂Cl. In an even further aspect, R¹¹, when present, is selected from —CF₃, —CHF₂, —CH₂F, —CH₂CH₂F, —CCl₃, —CHCl₂, —CH₂Cl, and —CH₂CH₂Cl.

In a still further aspect, R¹¹, when present, is selected from —CF₃, —CHF₂, —CH₂F, —CCl₃, —CHCl₂, and —CH₂Cl.

In various aspects, R¹¹, when present, is Ar².

In various aspects, R¹¹, when present, is —(C1-C10 alkyl)CO₂(C1-C10 alkyl).

In a further aspect, R¹¹, when present, is —(C1-C8 alkyl)CO₂(C1-C8 alkyl). In a still further aspect, R¹¹, when

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present, is —(C1-C4 alkyl)CO₂(C1-C4 alkyl). In yet a further aspect, R¹¹, when present, is selected from —CH₂CO₂CH₃, —CH₂CH₂CO₂CH₃, —CH₂CO₂CH₂CH₃, —CH₂CH₂CH₂CO₂CH₃, and —CH(CH₃)CH₂CO₂CH₃. In an even further aspect, R¹¹, when present, is selected from —CH₂CO₂CH₃, —CH₂CH₂CO₂CH₃, and —CH₂CO₂CH₂CH₃. In a still further aspect, R¹¹, when present, is —CH₂CO₂CH₃.

In various aspects, R¹¹, when present, is selected from —(C1-C10 alkyl)CO₂(C1-C10 alkylthiol) and —(C1-C10 alkyl)-S—S—(C1-C10 alkyl). In a further aspect, R¹¹, when present, is selected from —(C1-C8 alkyl)CO₂(C1-C8 alkylthiol) and —(C1-C8 alkyl)-S—S—(C1-C8 alkyl). In a still further aspect, R¹¹, when present, is selected from —(C1-C4 alkyl)CO₂(C1-C4 alkylthiol) and —(C1-C4 alkyl)-S—S—(C1-C4 alkyl). In yet a further aspect, R¹¹, when present, is selected from —CH₂CO₂CH₂SH, —CH₂CH₂CO₂CH₂SH, —CH₂CO₂CH₂CH₂SH, —CH₂CH₂CH₂CO₂CH₂SH, —CH(CH₃)CH₂CO₂CH₂SH, —CH₂—S—S—CH₃, —CH₂CH₂—S—S—CH₃, —CH₂—S—S—CH₂CH₃, —CH₂CH₂CH₂—S—S—CH₃, and —CH(CH₃)CH₂—S—S—CH₃. In an even further aspect, R¹¹, when present, is selected from —CH₂CO₂CH₂SH, —CH₂CH₂CO₂CH₂SH, —CH₂CO₂CH₂CH₂SH, —CH₂—S—S—CH₃, —CH₂CH₂—S—S—CH₃, and —CH₂—S—S—CH₂CH₃. In a still further aspect, R¹¹, when present, is selected from —CH₂CO₂CH₂SH and —CH₂—S—S—CH₃.

f. R¹² Groups

In one aspect, R¹², when present, is selected from hydrogen and C1-C8 alkyl. In a further aspect, R¹², when present, is selected from hydrogen and C1-C8 alkyl. In a still further aspect, R¹², when present, is selected from hydrogen and C1-C6 alkyl. In yet a further aspect, R¹², when present, is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. In an even further aspect, R¹², when present, is selected from hydrogen, methyl, ethyl, n-propyl, and isopropyl. In a still further aspect, R¹², when present, is selected from hydrogen, methyl, and ethyl. In yet a further aspect, R¹², when present, is selected from hydrogen and ethyl. In an even further aspect, R¹², when present, is selected from hydrogen and methyl.

In various aspects, R¹², when present, is C1-C10 alkyl. In a further aspect, R¹², when present, is C1-C8 alkyl. In a still further aspect, R¹², when present, is C1-C6 alkyl. In yet a further aspect, R¹², when present, is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. In an even further aspect, R¹², when present, is methyl, ethyl, n-propyl, and isopropyl. In a still further aspect, R¹², when present, is methyl and ethyl. In yet a further aspect, R¹², when present, is ethyl. In an even further aspect, R¹³, when present, is methyl.

In a further aspect, R¹², when present, is hydrogen.

g. R¹³ Groups

In one aspect, R¹³, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar³. In a further aspect, R¹³, when present, is selected from C1-C8 alkyl, C3-C8 cycloalkyl, and Ar³. In a still further aspect, R¹³, when present, is selected from C1-C4 alkyl, C3-C4 cycloalkyl, and Ar³. In yet a further aspect, R¹³, when present, is selected from methyl, ethyl, n-propyl, isopropyl, cyclopropyl, and Ar³. In an even further aspect, R¹³, when present, is selected from methyl, ethyl, and Ar³. In a still further aspect, R¹³, when present, is selected from methyl and Ar³.

In various aspects, R¹³, when present, is C1-C10 alkyl. In a further aspect, R¹³, when present, is C1-C8 alkyl. In a still further aspect, R¹³, when present, is C1-C4 alkyl. In yet a

further aspect, R^{13} , when present, is selected from methyl, ethyl, n-propyl, and isopropyl. In an even further aspect, R^{13} , when present, is selected from methyl and ethyl. In a still further aspect, R^{13} , when present, is ethyl. In yet a further aspect, R^{13} , when present, is methyl.

In various aspects, R^{13} , when present, is C3-C10 cycloalkyl. In a further aspect, R^{13} , when present, is C3-C8 cycloalkyl. In a still further aspect, R^{13} , when present, is selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In yet a further aspect, R^{13} , when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl. In an even further aspect, R^{13} , when present, is selected from cyclopropyl and cyclobutyl. In a still further aspect, R^{13} , when present, is cyclobutyl.

In various aspects, R^{13} , when present, is Ar^3 .

h. R^4 Groups

In one aspect, R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{21}$. In a further aspect, R^{14} , when present, is selected from C1-C15 alkyl, C2-C15 alkenyl, and $-CH(NH_2)R^{21}$. In a still further aspect, R^{14} , when present, is selected from C1-C8 alkyl, C2-C8 alkenyl, and $-CH(NH_2)R^{21}$. In yet a further aspect, R^{14} , when present, is selected from C1-C4 alkyl, C2-C4 alkenyl, and $-CH(NH_2)R^{21}$. In an even further aspect, R^{14} , when present, is selected from methyl, ethyl, isopropyl, n-propyl, ethenyl, propenyl, and $-CH(NH_2)R^{21}$. In a still further aspect, R^{14} , when present, is selected from methyl, ethyl, isopropyl, ethenyl, and $-CH(NH_2)R^{21}$. In yet a further aspect, R^{14} , when present, is selected from methyl and $-CH(NH_2)R^{21}$.

In a further aspect, R^{14} , when present, is selected from C1-C30 alkyl and C2-C30 alkenyl. In a still further aspect, R^{14} , when present, is selected from C1-C15 alkyl and C2-C15 alkenyl. In yet a further aspect, R^{14} , when present, is selected from C1-C8 alkyl and C2-C8 alkenyl. In an even further aspect, R^{14} , when present, is selected from C1-C4 alkyl and C2-C4 alkenyl. In a still further aspect, R^{14} , when present, is selected from methyl, ethyl, isopropyl, n-propyl, ethenyl, and isopropenyl. In yet a further aspect, R^{14} , when present, is selected from methyl, ethyl, and ethenyl.

In a further aspect, R^{14} , when present, is selected from C1-C30 alkyl and $-CH(NH_2)R^{21}$. In a still further aspect, R^{14} , when present, is selected from C1-C15 alkyl and $-CH(NH_2)R^{21}$. In yet a further aspect, R^{14} , when present, is selected from C1-C8 alkyl and $-CH(NH_2)R^{21}$. In an even further aspect, R^{14} , when present, is selected from C1-C4 alkyl and $-CH(NH_2)R^{21}$. In a still further aspect, R^{14} , when present, is selected from methyl, ethyl, isopropyl, n-propyl, and $-CH(NH_2)R^{21}$. In yet a further aspect, R^{14} , when present, is selected from methyl, ethyl, and $-CH(NH_2)R^{21}$. In an even further aspect, R^{14} , when present, is selected from methyl and $-CH(NH_2)R^{21}$.

In a further aspect, R^{14} , when present, is selected from C2-C30 alkenyl and $-CH(NH_2)R^{21}$. In a still further aspect, R^{14} , when present, is selected from C2-C15 alkenyl and $-CH(NH_2)R^{21}$. In yet a further aspect, R^{14} , when present, is selected from C2-C8 alkenyl and $-CH(NH_2)R^{21}$. In an even further aspect, R^{14} , when present, is selected from C2-C4 alkenyl and $-CH(NH_2)R^{21}$. In a still further aspect, R^{14} , when present, is selected from ethenyl, propenyl, and $-CH(NH_2)R^{21}$. In yet a further aspect, R^{14} , when present, is selected from ethenyl and $-CH(NH_2)R^{21}$.

In a further aspect, R^{14} , when present, is C1-C30 alkyl. In a still further aspect, R^{14} , when present, is C1-C15 alkyl. In yet a further aspect, R^{14} , when present, is C1-C8 alkyl. In an even further aspect, R^{14} , when present, is C1-C4 alkyl. In a still further aspect, R^{14} , when present, is selected from

methyl, ethyl, isopropyl, and n-propyl. In yet a further aspect, R^{14} , when present, is selected from methyl and ethyl. In an even further aspect, R^{14} , when present, is ethyl. In a still further aspect, R^{14} , when present, is methyl.

5 In a further aspect, R^{14} , when present, is C2-C30 alkenyl. In a still further aspect, R^{10} , when present, is C2-C15 alkenyl. In yet a further aspect, R^{14} , when present, is C2-C8 alkenyl. In an even further aspect, R^{14} , when present, is C2-C4 alkenyl. In a still further aspect, R^{14} , when present, is selected from ethenyl and propenyl. In yet a further aspect, R^{14} , when present, is propenyl. In an even further aspect, R^{14} , when present, is ethenyl.

In a further aspect, R^{14} , when present, is $-CH(NH_2)R^{21}$.

15 i. R^{20} Groups

In one aspect, R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(C1-C8 \text{ alkyl})NHC(NH)NH_2$, $-(C1-C8 \text{ alkyl})CO_2H$, $-(C1-C8 \text{ alkyl})C(O)NH_2$, Cy^1 , and $-(C1-C8 \text{ alkyl})Cy^1$. In a further aspect, R^{20} , when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 hydroxyalkyl, C1-C4 alkylthiol, C1-C4 aminoalkyl, C1-C4 alkylselenide, $-(C1-C4 \text{ alkyl})NHC(NH)NH_2$, $-(C1-C4 \text{ alkyl})CO_2H$, $-(C1-C4 \text{ alkyl})C(O)NH_2$, Cy^1 , and $-(C1-C4 \text{ alkyl})Cy^1$. In a still further aspect, R^{20} , when present, is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2SH$, $-CH_2CH_2SH$, $-CH(CH_3)CH_2SH$, $-CH_2CH_2CH_2SH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH(CH_3)CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2SeH$, $-CH_2CH_2SeH$, $-CH(CH_3)CH_2SeH$, $-CH_2CH_2CH_2SeH$, $-CH_2NHC(NH)NH_2$, $-CH_2CH_2NHC(NH)NH_2$, $-CH(CH_3)CH_2NHC(NH)NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH(CH_3)CH_2CO_2H$, $-CH_2CH_2CH_2CO_2H$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, $-CH(CH_3)CH_2C(O)NH_2$, $-CH_2CH_2CH_2C(O)NH_2$, Cy^1 , $-CH_2Cy^1$, $-CH_2CH_2Cy^1$, $-CH(CH_3)CH_2Cy^1$, and $-CH_2CH_2CH_2Cy^1$. In yet a further aspect, R^{20} , when present, is selected from hydrogen, methyl, ethyl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2SH$, $-CH_2CH_2SH$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2SeH$, $-CH_2CH_2SeH$, $-CH_2NHC(NH)NH_2$, $-CH_2CH_2NHC(NH)NH_2$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2C(O)NH_2$, $-CH_2CH_2C(O)NH_2$, Cy^1 , $-CH_2Cy^1$, and $-CH_2CH_2Cy^1$.

35 In an even further aspect, R^{20} , when present, is selected from hydrogen, methyl, $-CH_2OH$, $-CH_2SH$, $-CH_2NH_2$, $-CH_2SeH$, $-CH_2NHC(NH)NH_2$, $-CH_2CO_2H$, $-CH_2C(O)NH_2$, Cy^1 , and $-CH_2Cy^1$.

40 In various aspects, R^{20} , when present, is selected from hydrogen and C1-C8 alkyl. In a further aspect, R^{20} , when present, is selected from hydrogen and C1-C4 alkyl. In a still further aspect, R^{20} , when present, is selected from hydrogen, methyl, ethyl, n-propyl, and isopropyl. In yet a further aspect, R^{20} , when present, is selected from hydrogen, methyl, and ethyl. In an even further aspect, R^{20} , when present, is selected from hydrogen and methyl.

In various aspects, R^{20} , when present, is selected from hydrogen, C1-C8 hydroxyalkyl, and $-(C1-C8 \text{ alkyl})CO_2H$. In a further aspect, R^{20} , when present, is selected from hydrogen, C1-C4 hydroxyalkyl, and $-(C1-C4 \text{ alkyl})CO_2H$. In a still further aspect, R^{20} , when present, is selected from hydrogen, $-CH_2OH$, $-CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH(CH_3)CH_2CO_2H$, and $-CH_2CH_2CH_2CO_2H$. In yet a further aspect, R^{20} , when present, is selected from hydrogen, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CO_2H$, and

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—CH₂CH₂CO₂H. In an even further aspect, R²⁰, when present, is selected from hydrogen, —CH₂OH, and —CH₂CO₂H.

In various aspects, R²⁰, when present, is selected from hydrogen, C1-C8 alkylthiol, and C1-C8 alkylselenide. In a further aspect, R²⁰, when present, is selected from hydrogen, C1-C4 alkylthiol, and C1-C4 alkylselenide. In a still further aspect, R²⁰, when present, is selected from hydrogen, —CH₂SH, —CH₂CH₂SH, —CH(CH₃)CH₂SH, —CH₂CH₂CH₂SH, —CH₂SeH, —CH₂CH₂SeH, —CH(CH₃)CH₂SeH, and —CH₂CH₂CH₂SeH. In yet a further aspect, R²⁰, when present, is selected from hydrogen, —CH₂SH, —CH₂CH₂SH, —CH₂SeH, and —CH₂CH₂SeH. In an even further aspect, R²⁰, when present, is selected from hydrogen, —CH₂SH, and —CH₂SeH.

In various aspects, R²⁰, when present, is selected from hydrogen, C1-C8 aminoalkyl, —(C1-C8 alkyl)NHC(NH)NH₂, and —(C1-C8 alkyl)C(O)NH₂. In a further aspect, R²⁰, when present, is selected from hydrogen, C1-C4 aminoalkyl, —(C1-C4 alkyl)NHC(NH)NH₂, and —(C1-C4 alkyl)C(O)NH₂. In a still further aspect, R²⁰, when present, is selected from hydrogen, —CH₂NH₂, —CH₂CH₂NH₂, —CH(CH₃)CH₂NH₂, —CH₂CH₂CH₂NH₂, —CH₂NHC(NH)NH₂, —CH₂CH₂NHC(NH)NH₂, —CH(CH₃)CH₂NHC(NH)NH₂, —CH₂CH₂CH₂NHC(NH)NH₂, —CH₂C(O)NH₂, —CH₂CH₂C(O)NH₂, —CH(CH₃)CH₂C(O)NH₂, and —CH₂CH₂CH₂C(O)NH₂. In yet a further aspect, R²⁰, when present, is selected from hydrogen, —CH₂NH₂, —CH₂CH₂NH₂, —CH₂NHC(NH)NH₂, —CH₂CH₂NHC(NH)NH₂, —CH₂C(O)NH₂, and —CH₂CH₂C(O)NH₂. In an even further aspect, R²⁰, when present, is selected from hydrogen, —CH₂NH₂, —CH₂NHC(NH)NH₂, and —CH₂C(O)NH₂.

In various aspects, R²⁰, when present, is selected from hydrogen, Cy¹, and —(C1-C8 alkyl)Cy¹. In a further aspect, R²⁰, when present, is selected from hydrogen, Cy¹, and —(C1-C4 alkyl)Cy¹. In a still further aspect, R²⁰, when present, is selected from hydrogen, Cy¹, —CH₂Cy¹, —CH₂CH₂Cy¹, —CH(CH₃)CH₂Cy¹, and —CH₂CH₂CH₂Cy¹. In yet a further aspect, R²⁰, when present, is selected from hydrogen, Cy¹, —CH₂Cy¹, and —CH₂CH₂Cy¹. In an even further aspect, R²⁰, when present, is selected from hydrogen, Cy¹, and —CH₂Cy¹.

In various aspects, R²⁰, when present, is C1-C8 alkyl. In a further aspect, R²⁰, when present, is C1-C4 alkyl. In a still further aspect, R²⁰, when present, is selected from methyl, ethyl, n-propyl, and isopropyl. In yet a further aspect, R²⁰, when present, is selected from methyl and ethyl. In an even further aspect, R²⁰, when present, is methyl.

In various aspects, R²⁰, when present, is hydrogen.

j. R²¹ Groups

In one aspect, R²¹, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, —(C1-C8 alkyl)NHC(NH)NH₂, —(C1-C8 alkyl)CO₂H, —(C1-C8 alkyl)C(O)NH₂, Cy³, and —(C1-C8 alkyl)Cy³. In a further aspect, R²¹, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 hydroxyalkyl, C1-C4 alkylthiol, C1-C4 aminoalkyl, C1-C4 alkylselenide, —(C1-C4 alkyl)NHC(NH)NH₂, —(C1-C4 alkyl)CO₂H, —(C1-C4 alkyl)C(O)NH₂, Cy³, and —(C1-C4 alkyl)Cy³. In a still further aspect, R²¹, when present, is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, —CH₂OH, —CH₂CH₂OH, —CH(CH₃)CH₂OH, —CH₂CH₂CH₂OH, —CH₂SH, —CH₂CH₂SH, —CH(CH₃)CH₂SH, —CH₂CH₂CH₂SH, —CH₂NH₂, —CH₂CH₂NH₂, —CH(CH₃)CH₂NH₂, —CH₂CH₂CH₂NH₂, —CH₂SeH, —CH₂CH₂SeH, —CH(CH₃)CH₂SeH, —CH₂CH₂CH₂SeH,

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—CH₂NHC(NH)NH₂, —CH₂CH₂NHC(NH)NH₂, —CH(CH₃)CH₂NHC(NH)NH₂, —CH₂CH₂CH₂NHC(NH)NH₂, —CH₂CO₂H, —CH₂CH₂CO₂H, —CH(CH₃)CH₂CO₂H, —CH₂CH₂CH₂CO₂H, —CH₂C(O)NH₂, —CH₂CH₂C(O)NH₂, —CH(CH₃)CH₂C(O)NH₂, —CH₂CH₂CH₂C(O)NH₂, Cy³, —CH₂Cy³, —CH₂CH₂Cy³, —CH(CH₃)CH₂Cy³, and —CH₂CH₂CH₂Cy³. In yet a further aspect, R²¹, when present, is selected from hydrogen, methyl, ethyl, —CH₂OH, —CH₂CH₂OH, —CH₂SH, —CH₂CH₂SH, —CH₂NH₂, —CH₂CH₂NH₂, —CH₂SeH, —CH₂CH₂SeH, —CH₂NHC(NH)NH₂, —CH₂CH₂NHC(NH)NH₂, —CH₂CO₂H, —CH₂CH₂CO₂H, —CH₂C(O)NH₂, —CH₂CH₂C(O)NH₂, Cy³, —CH₂Cy³, and —CH₂CH₂Cy³. In an even further aspect, R²¹, when present, is selected from hydrogen, methyl, —CH₂OH, —CH₂SH, —CH₂NH₂, —CH₂SeH, —CH₂NHC(NH)NH₂, —CH₂CO₂H, —CH₂C(O)NH₂, Cy³, and —CH₂Cy³.

In various aspects, R²¹, when present, is selected from hydrogen and C1-C8 alkyl. In a further aspect, R²¹, when present, is selected from hydrogen and C1-C4 alkyl. In a still further aspect, R²¹, when present, is selected from hydrogen, methyl, ethyl, n-propyl, and isopropyl. In yet a further aspect, R²¹, when present, is selected from hydrogen, methyl, and ethyl. In an even further aspect, R²¹, when present, is selected from hydrogen and methyl.

In various aspects, R²¹, when present, is selected from hydrogen, C1-C8 hydroxyalkyl, and —(C1-C8 alkyl)CO₂H. In a further aspect, R²¹, when present, is selected from hydrogen, C1-C4 hydroxyalkyl, and —(C1-C4 alkyl)CO₂H. In a still further aspect, R²¹, when present, is selected from hydrogen, —CH₂OH, —CH₂CH₂OH, —CH(CH₃)CH₂OH, —CH₂CH₂CH₂OH, —CH₂CO₂H, —CH₂CH₂CO₂H, —CH(CH₃)CH₂CO₂H, and —CH₂CH₂CH₂CO₂H. In yet a further aspect, R²¹, when present, is selected from hydrogen, —CH₂OH, —CH₂CH₂OH, —CH₂CO₂H, and —CH₂CH₂CO₂H. In an even further aspect, R²¹, when present, is selected from hydrogen, —CH₂OH, and —CH₂CO₂H.

In various aspects, R²¹, when present, is selected from hydrogen, C1-C8 alkylthiol, and C1-C8 alkylselenide. In a further aspect, R²¹, when present, is selected from hydrogen, C1-C4 alkylthiol, and C1-C4 alkylselenide. In a still further aspect, R²¹, when present, is selected from hydrogen, —CH₂SH, —CH₂CH₂SH, —CH(CH₃)CH₂SH, —CH₂CH₂CH₂SH, —CH₂SeH, —CH₂CH₂SeH, —CH(CH₃)CH₂SeH, and —CH₂CH₂CH₂SeH. In yet a further aspect, R²¹, when present, is selected from hydrogen, —CH₂SH, —CH₂CH₂SH, —CH₂SeH, and —CH₂CH₂SeH. In an even further aspect, R²¹, when present, is selected from hydrogen, —CH₂SH, and —CH₂SeH.

In various aspects, R²¹, when present, is selected from hydrogen, C1-C8 aminoalkyl, —(C1-C8 alkyl)NHC(NH)NH₂, and —(C1-C8 alkyl)C(O)NH₂. In a further aspect, R²¹, when present, is selected from hydrogen, C1-C4 aminoalkyl, —(C1-C4 alkyl)NHC(NH)NH₂, and —(C1-C4 alkyl)C(O)NH₂. In a still further aspect, R²¹, when present, is selected from hydrogen, —CH₂NH₂, —CH₂CH₂NH₂, —CH(CH₃)CH₂NH₂, —CH₂CH₂CH₂NH₂, —CH₂NHC(NH)NH₂, —CH₂CH₂NHC(NH)NH₂, —CH(CH₃)CH₂NHC(NH)NH₂, —CH₂CH₂CH₂NHC(NH)NH₂, —CH₂C(O)NH₂, —CH₂CH₂C(O)NH₂, —CH(CH₃)CH₂C(O)NH₂, and —CH₂CH₂CH₂C(O)NH₂. In yet a further aspect, R²¹, when present, is selected from hydrogen, —CH₂NH₂, —CH₂CH₂NH₂, —CH₂NHC(NH)NH₂, —CH₂CH₂NHC(NH)NH₂, —CH₂C(O)NH₂, and —CH₂CH₂C(O)NH₂. In an even further aspect, R²¹, when

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present, is selected from hydrogen, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{NHC}(\text{NH})\text{NH}_2$, and $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$.

In various aspects, R^{21} , when present, is selected from hydrogen, Cy^3 , and $-(\text{C}1-\text{C}8 \text{ alkyl})\text{Cy}^3$. In a further aspect, R^{21} , when present, is selected from hydrogen, Cy^3 , and $-(\text{C}1-\text{C}4 \text{ alkyl})\text{Cy}^3$. In a still further aspect, R^{21} , when present, is selected from hydrogen, Cy^3 , $-\text{CH}_2\text{Cy}^3$, $-\text{CH}_2\text{CH}_2\text{Cy}^3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{Cy}^3$, and $-\text{CH}_2\text{CH}_2\text{CH}_2\text{Cy}^3$. In yet a further aspect, R^{21} , when present, is selected from hydrogen, Cy^3 , $-\text{CH}_2\text{Cy}^3$, and $-\text{CH}_2\text{CH}_2\text{Cy}^3$. In an even further aspect, R^{21} , when present, is selected from hydrogen, Cy^3 , and $-\text{CH}_2\text{Cy}^3$.

In various aspects, R^{21} , when present, is C1-C8 alkyl. In a further aspect, R^{21} , when present, is C1-C4 alkyl. In a still further aspect, R^{21} , when present, is selected from methyl, ethyl, n-propyl, and isopropyl. In yet a further aspect, R^{21} , when present, is selected from methyl and ethyl. In an even further aspect, R^{21} , when present, is methyl.

In various aspects, R^{21} , when present, is hydrogen.

k. Cy^1 Groups

In one aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a further aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, or 2 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0 or 1 group selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is monosubstituted with a group selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is unsubstituted.

In various aspects, Cy^1 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a further aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, or 2 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4

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alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0 or 1 group selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is monosubstituted with a group selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Cy^1 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is unsubstituted.

In various aspects, Cy^1 , when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C3-C6 cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicycle[4.4.0]hexane, and spiro[3.3]pentane. In a further aspect, Cy^1 , when present, is C3-C6 cycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy^1 , when present, is C3-C6 cycloalkyl substituted with 0 or 1 group selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Cy^1 , when present, is C3-C6 cycloalkyl monosubstituted with a group selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Cy^1 , when present, is unsubstituted C3-C6 cycloalkyl.

In various aspects, Cy^1 , when present, is C3-C6 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C3-C6 heterocycloalkyls include, but are not limited to, thietane, azetidine, oxetane, pyrrolidine, imidazolidine, tetrahydrothiophene, tetrahydrofuran, piperidine, piperazine, thiane, morpholine, and azaindole. In a further aspect, Cy^1 , when present, is C3-C6 heterocycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy^1 , when present, is C3-C6 heterocycloalkyl substituted with 0 or 1 group selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl,

noalkyl. In an even further aspect, Cy³, when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is unsubstituted.

In various aspects, Cy³, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C3-C6 cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicycle[4.4.0]hexane, and spiro [3.3]pentane. In a further aspect, Cy³, when present, is C3-C6 cycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy³, when present, is C3-C6 cycloalkyl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Cy³, when present, is C3-C6 cycloalkyl monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Cy³, when present, is unsubstituted C3-C6 cycloalkyl.

In various aspects, Cy³, when present, is C3-C6 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C3-C6 heterocycloalkyls include, but are not limited to, thietane, azetidine, oxetane, pyrrolidine, imidazolidine, tetrahydrothiophene, tetrahydrofuran, piperidine, piperazine, thiane, morpholine, and azaindole. In a further aspect, Cy³, when present, is C3-C6 heterocycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy³, when present, is C3-C6 heterocycloalkyl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Cy³, when present, is C3-C6 heterocycloalkyl monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Cy³, when present, is unsubstituted C3-C6 heterocycloalkyl.

In various aspects, Cy³, when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl,

C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a further aspect, Cy³, when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy³, when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Cy³, when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Cy³, when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is unsubstituted.

In various aspects, Cy³, when present, is C6-C14 aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C6-C14 aryls include, but are not limited to, phenyl, naphthyl, anthracenyl, and phenanthrenyl. In a further aspect, Cy³, when present, is C6-C14 aryl substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy³, when present, is C6-C14 aryl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Cy³, when present, is C6-C14 aryl monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Cy³, when present, is unsubstituted C6-C14 aryl.

In various aspects, Cy³, when present, is C2-C10 heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C2-C10 heteroaryls include, but are not limited to, thiophene, furan, pyrrole, oxazole, isoxazole, isothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, indole, azaindole, purine, benzofuran, quinolone, isoquinoline, and quinoxaline. In a further aspect, Cy³, when present, is C2-C10 heteroaryl substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl,

C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Cy^3 , when present, is C2-C10 heteroaryl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Cy^3 , when present, is C2-C10 heteroaryl monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Cy^3 , when present, is unsubstituted C2-C10 heteroaryl.

n. Ar¹ Groups

In one aspect, Ar¹ is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a further aspect, Ar¹ is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Ar¹ is selected from C6-C14 aryl and C2-C10 heteroaryl, and is monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Ar¹ is selected from C6-C14 aryl and C2-C10 heteroaryl, and is unsubstituted.

In various aspects, Ar¹ is C6-C14 aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C6-C14 aryls include, but are not limited to, phenyl, naphthyl, anthracenyl, and phenanthrenyl. In a further aspect, Ar¹ is C6-C14 aryl substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Ar¹ is C6-C14 aryl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Ar¹ is C6-C14 aryl monosubstituted with a group selected from halogen,

—CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Ar¹ is unsubstituted C6-C14 aryl.

In various aspects, Ar¹ is C6 aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a further aspect, Ar¹ is C6 aryl substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Ar¹ is C6 aryl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Ar¹ is C6 aryl monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Ar¹ is unsubstituted C6 aryl.

In various aspects, Ar¹ is C2-C10 heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C2-C10 heteroaryls include, but are not limited to, thiophene, furan, pyrrole, oxazole, isoxazole, isothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, indole, azaindole, purine, benzofuran, quinolone, isoquinoline, and quinoxaline. In a further aspect, Ar¹ is C2-C10 heteroaryl substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Ar¹ is C2-C10 heteroaryl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Ar¹ is unsubstituted C2-C10 heteroaryl.

o. Ar² Groups

In one aspect, Ar², when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a further aspect, Ar², when present, is selected from C6-C14 aryl and

aspect, Ar³, when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is unsubstituted.

In various aspects, Ar³, when present, is C6-C14 aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C6-C14 aryls include, but are not limited to, phenyl, naphthyl, anthracenyl, and phenanthrenyl. In a further aspect, Ar³, when present, is C6-C14 aryl substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Ar³, when present, is C6-C14 aryl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Ar³, when present, is C6-C14 aryl monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Ar³, when present, is unsubstituted C6-C14 aryl.

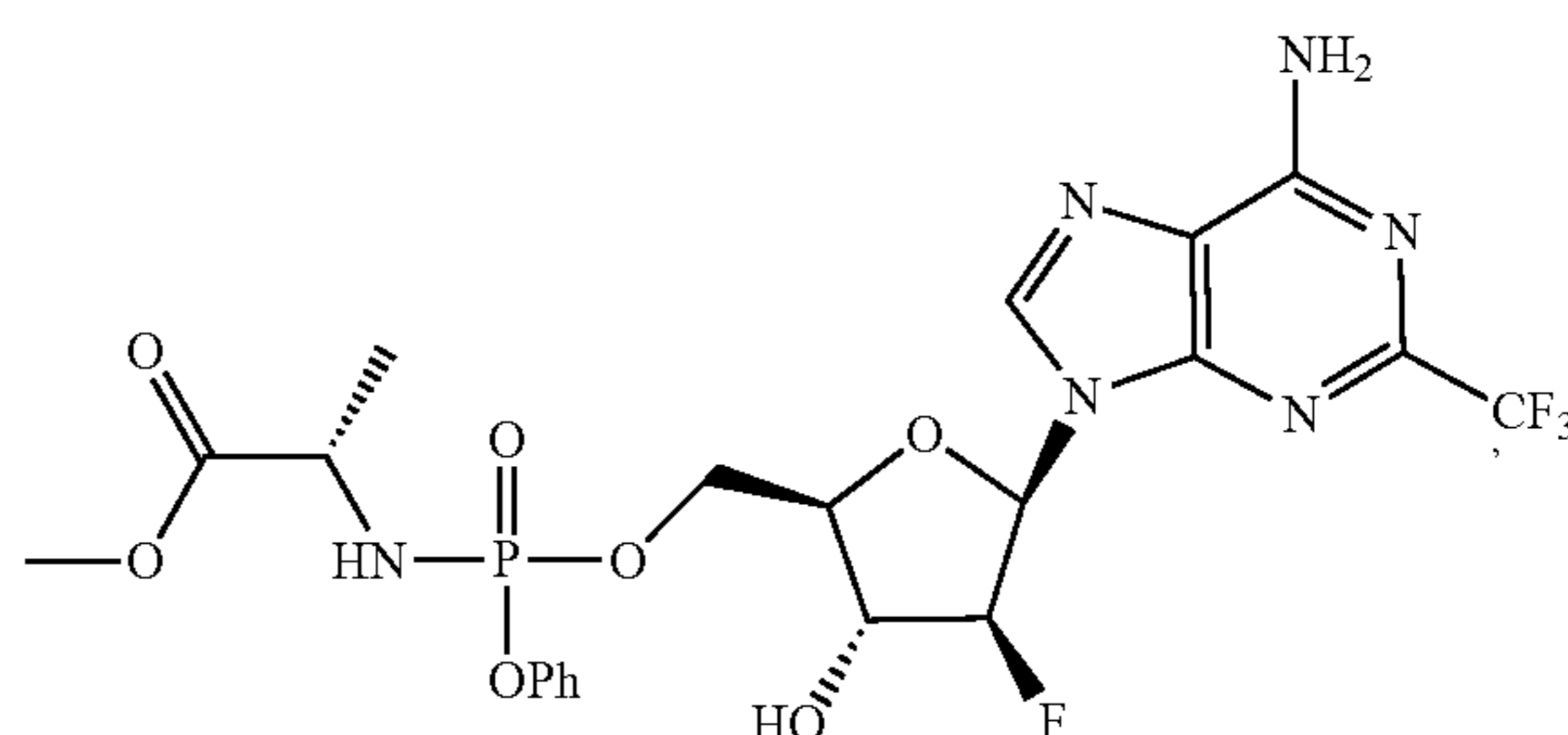
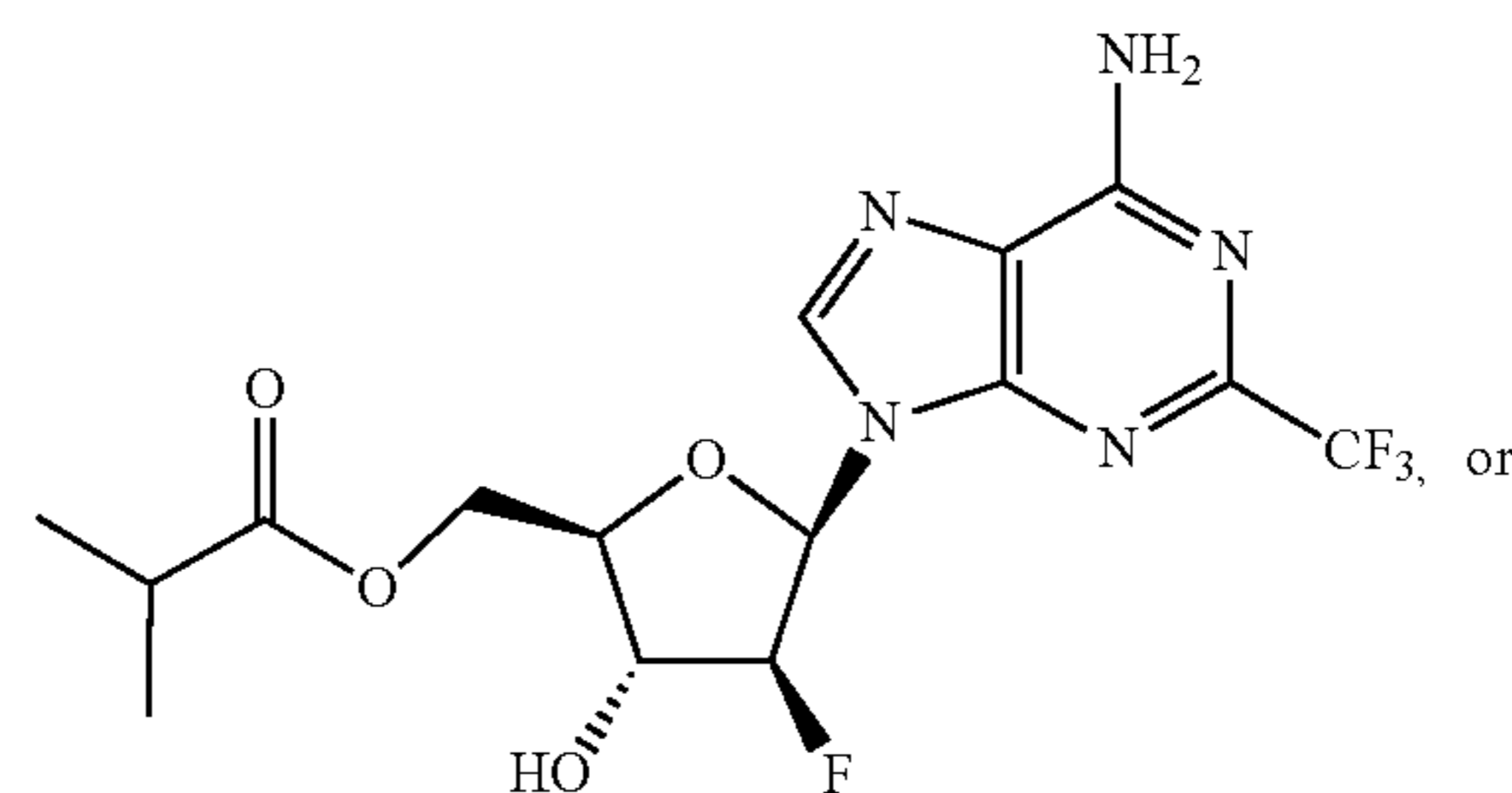
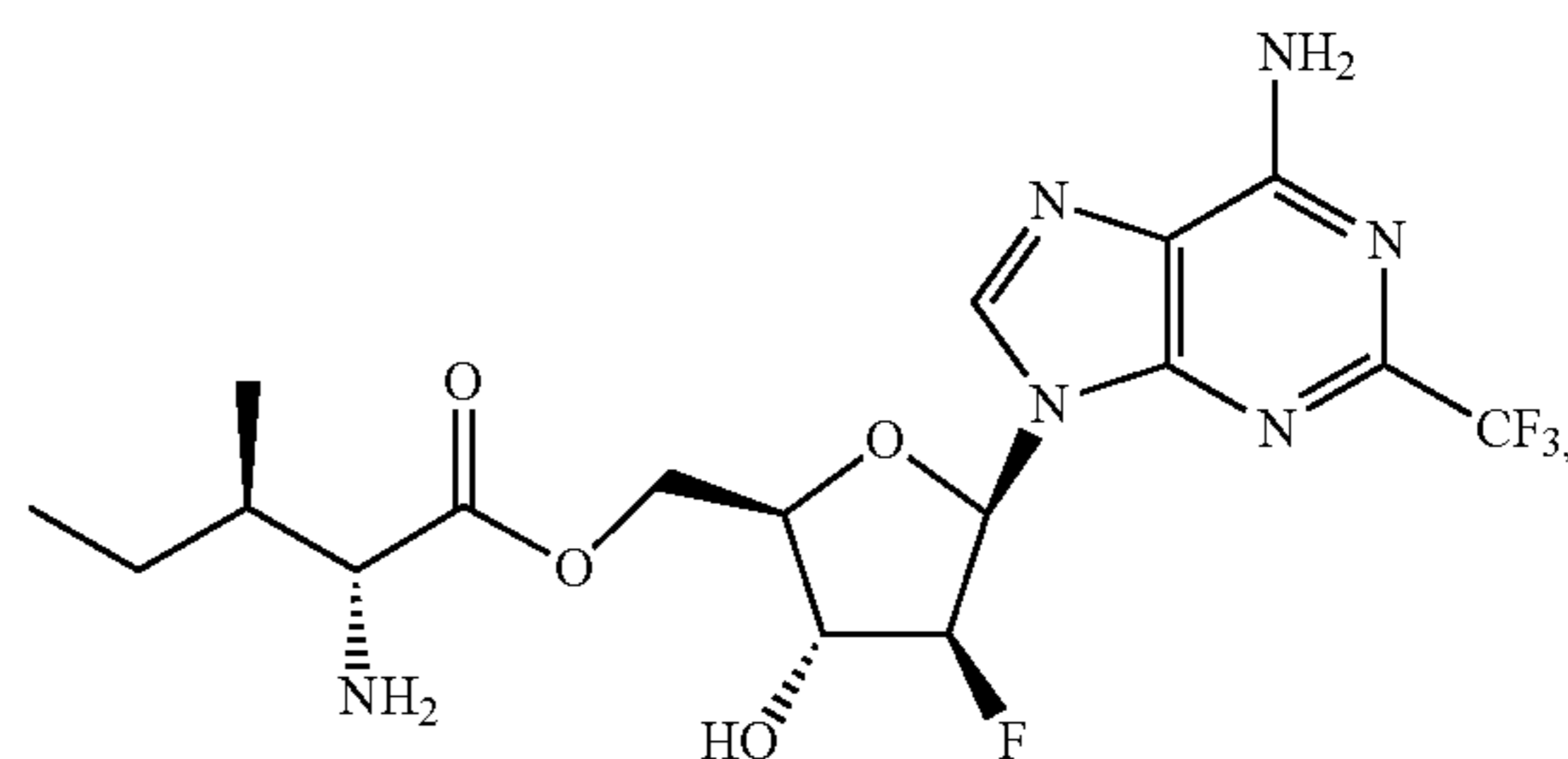
In various aspects, Ar³, when present, is C6 aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a further aspect, Ar³, when present, is C6 aryl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Ar³, when present, is C6 aryl monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Ar³, when present, is unsubstituted C6 aryl.

In various aspects, Ar³, when present, is C2-C10 heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. Examples of C2-C10 heteroaryls include, but are not limited to, thiophene, furan, pyrrole, oxazole, isoxazole, isothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, indole, azaindole, purine, benzofuran, quinolone, isoquinoline, and quinoxaline. In a further aspect, Ar³, when present, is C2-C10 heteroaryl

substituted with 0, 1, or 2 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In a still further aspect, Ar³, when present, is C2-C10 heteroaryl substituted with 0 or 1 group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In yet a further aspect, Ar³, when present, is C2-C10 heteroaryl monosubstituted with a group selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl. In an even further aspect, Ar³, when present, is unsubstituted C2-C10 heteroaryl.

2. Example Compounds

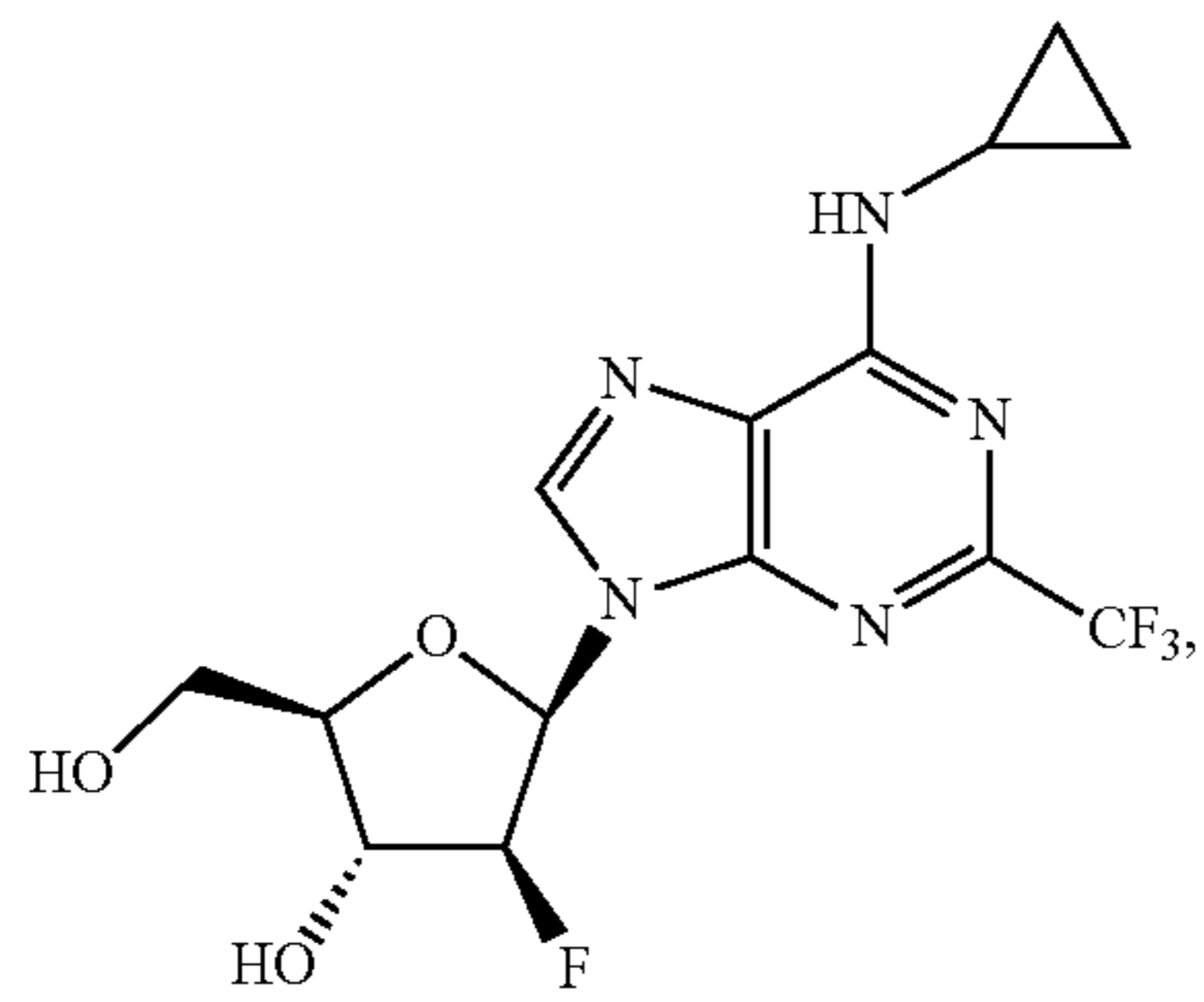
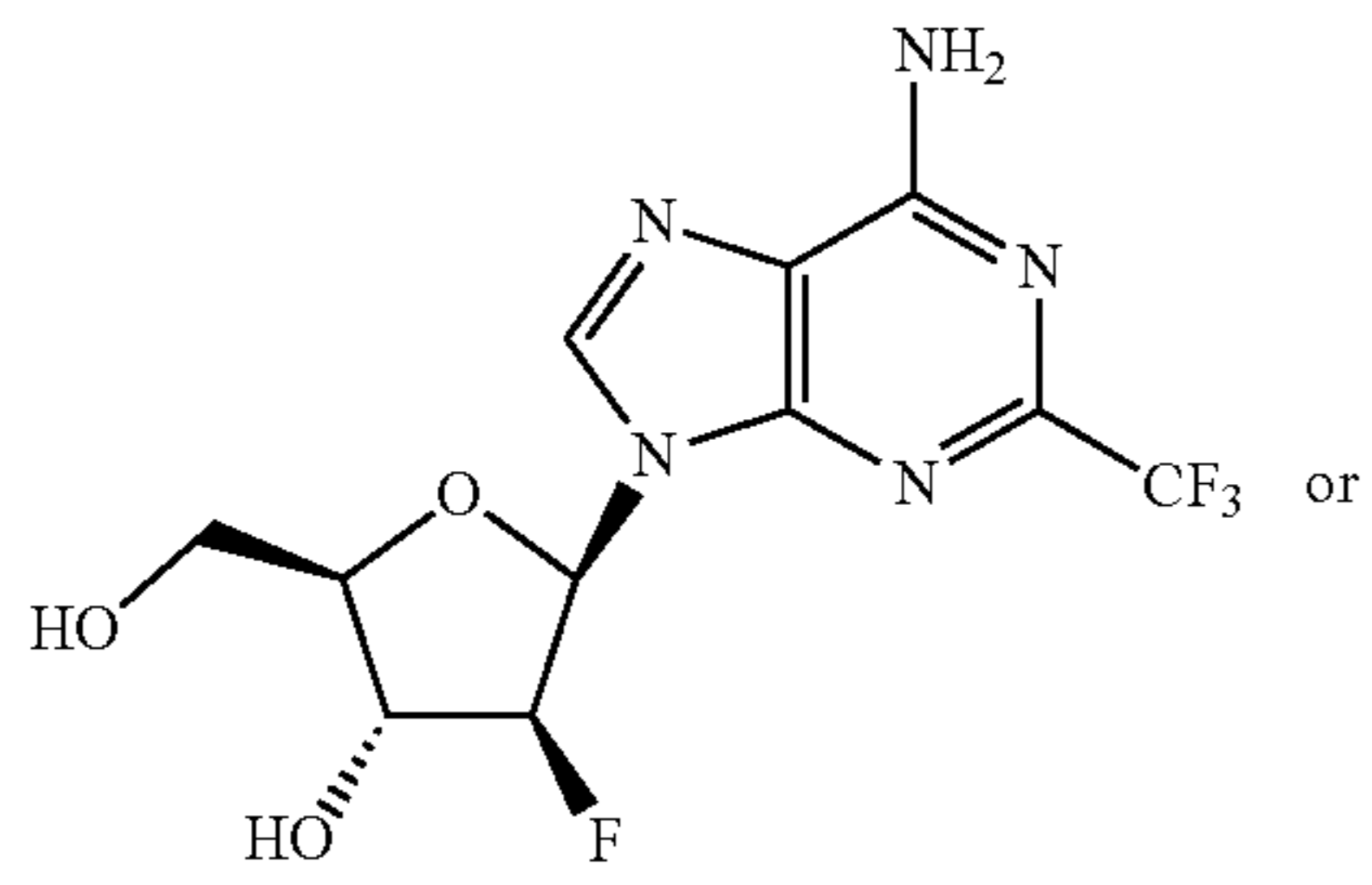
In one aspect, a compound can be present as:



or a pharmaceutically acceptable salt thereof.

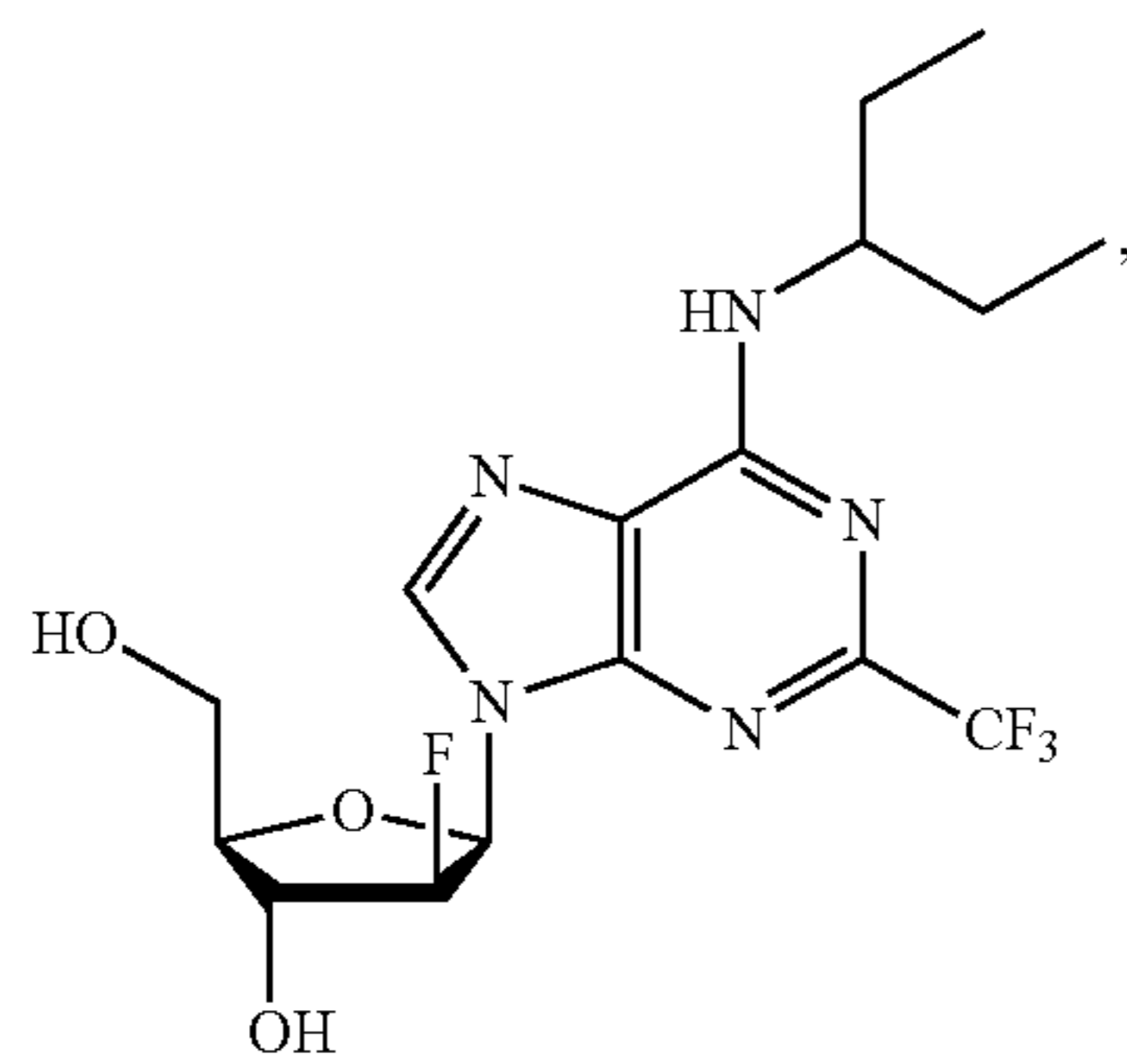
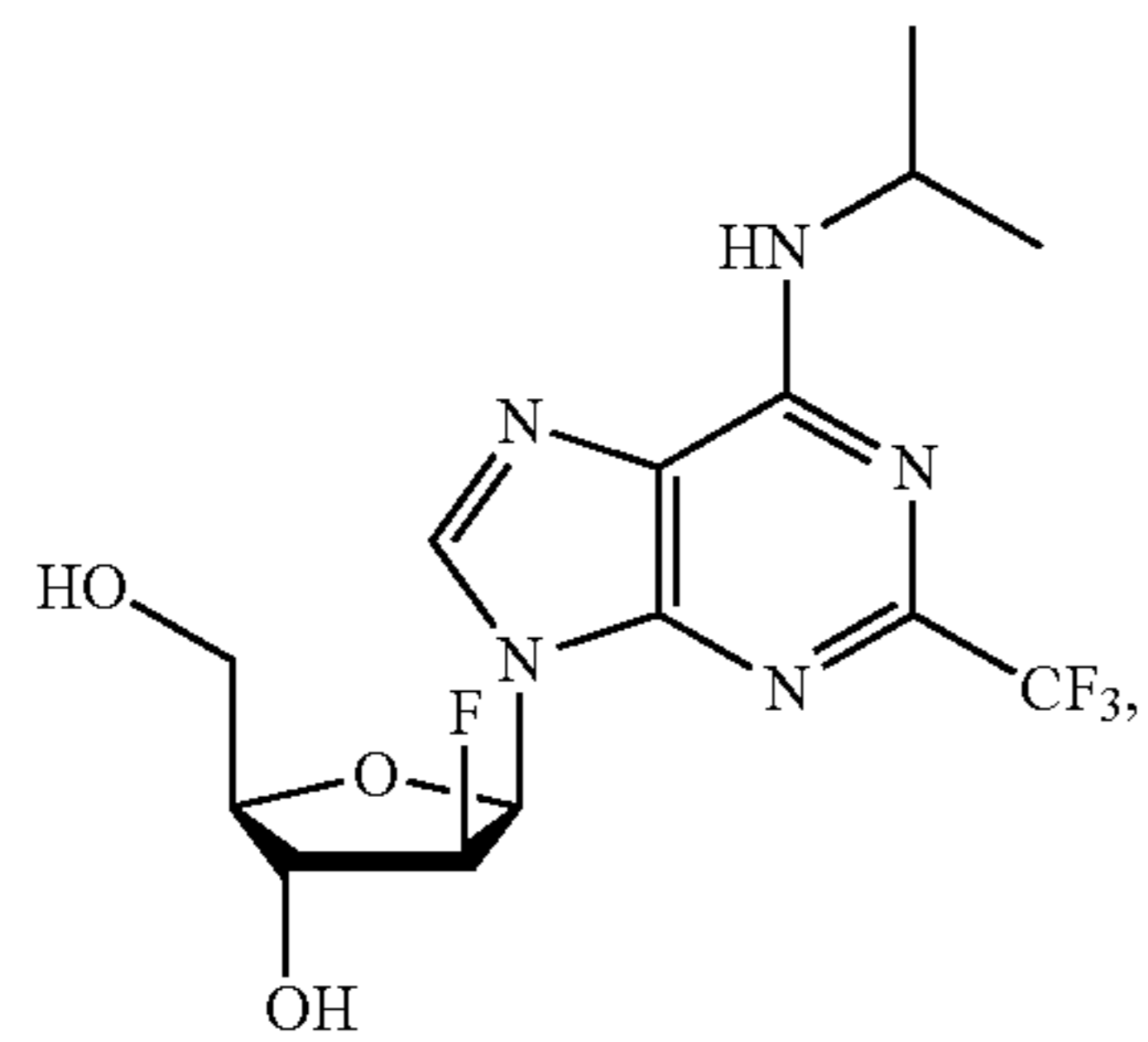
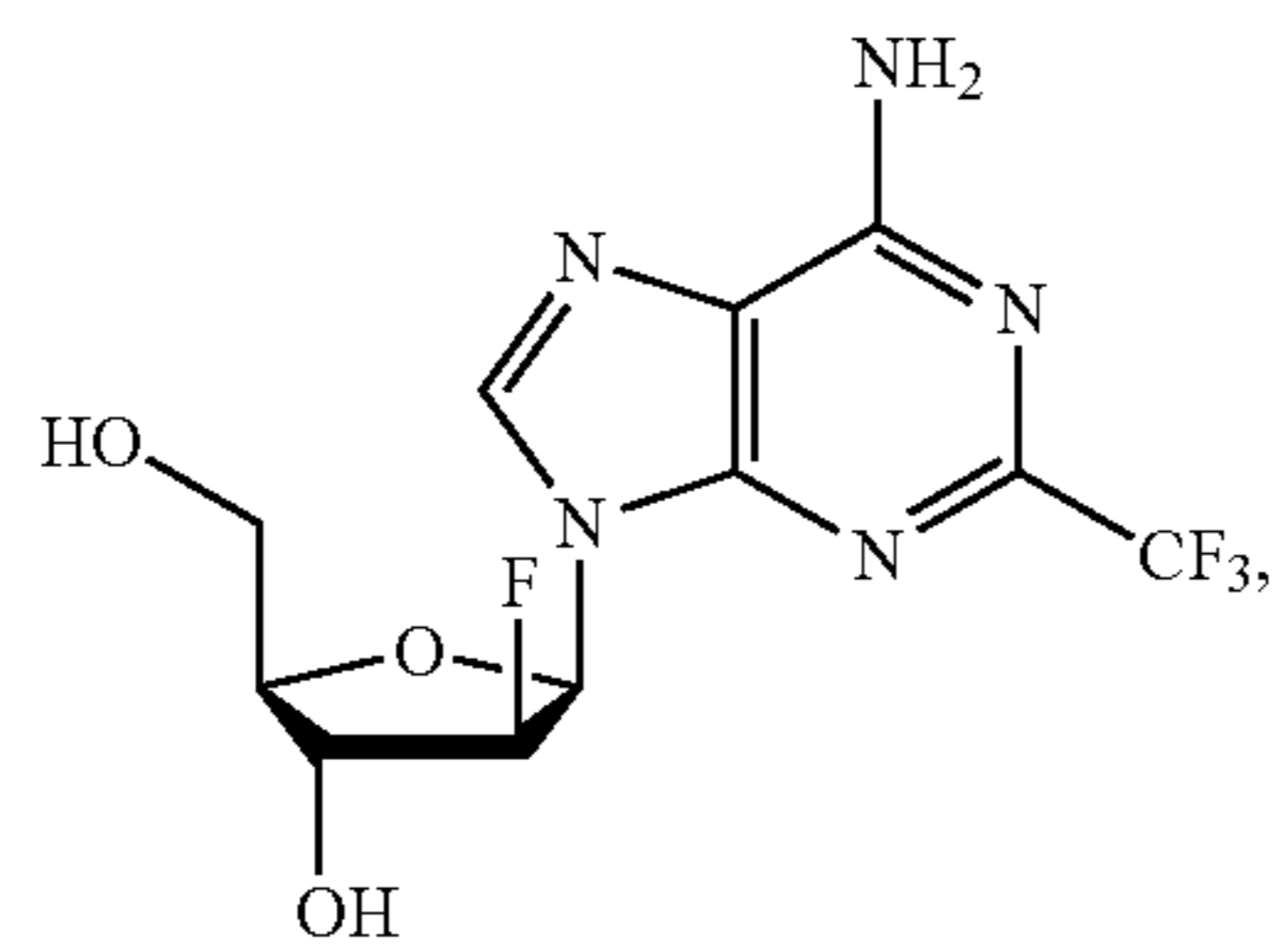
79

In one aspect, a compound can be present as:



or a pharmaceutically acceptable salt thereof.

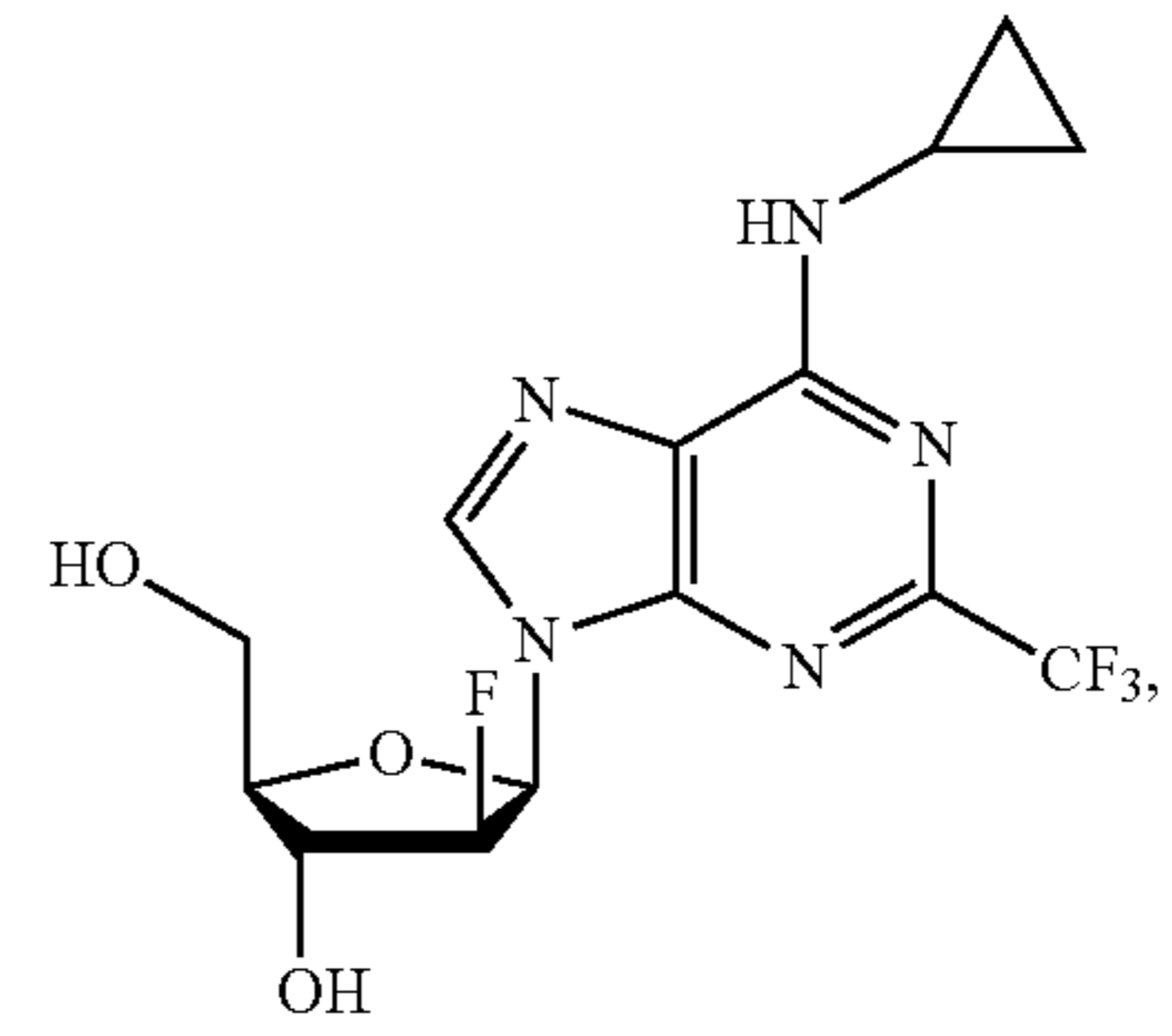
In one aspect, a compound can be present as:



80

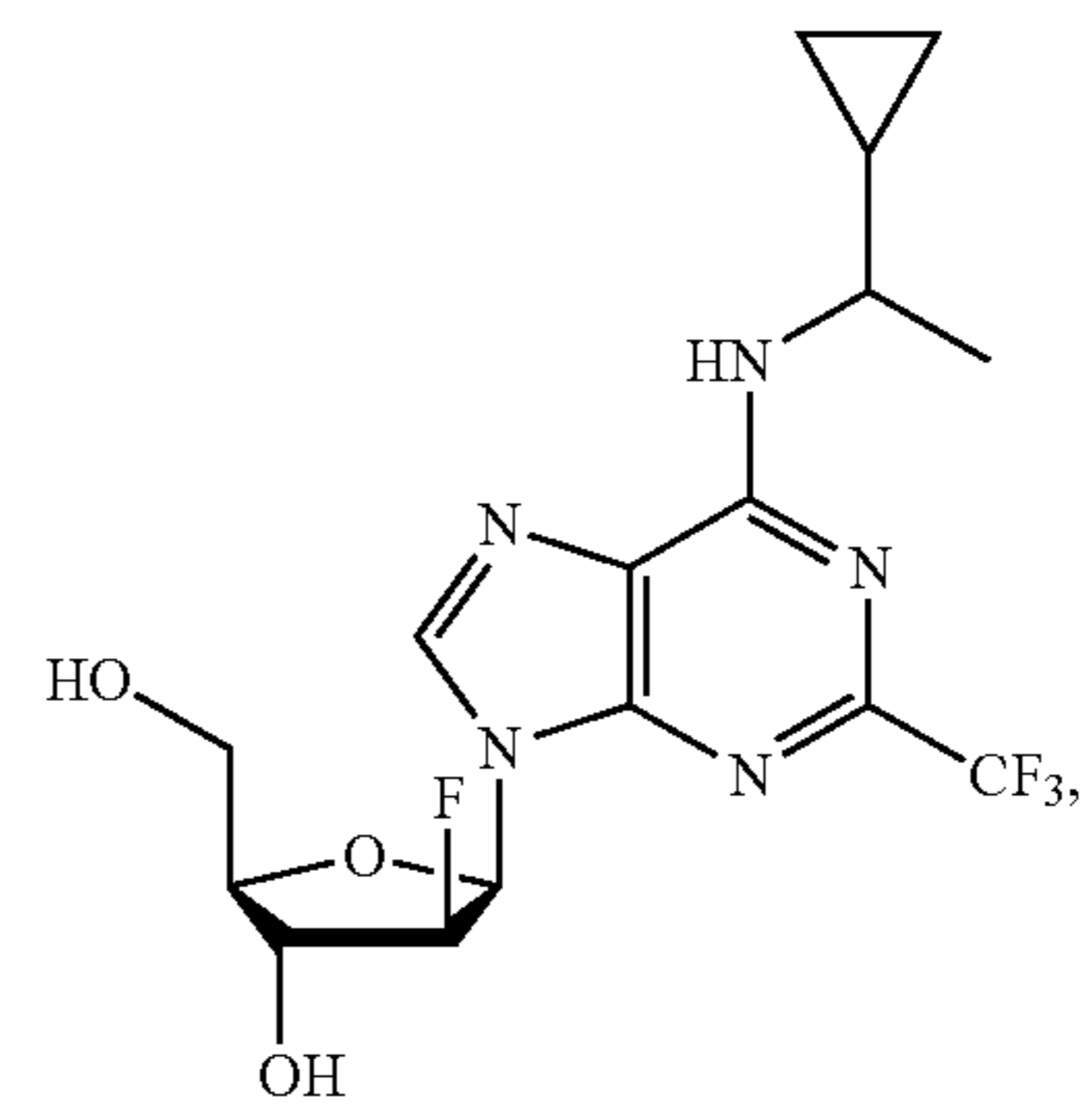
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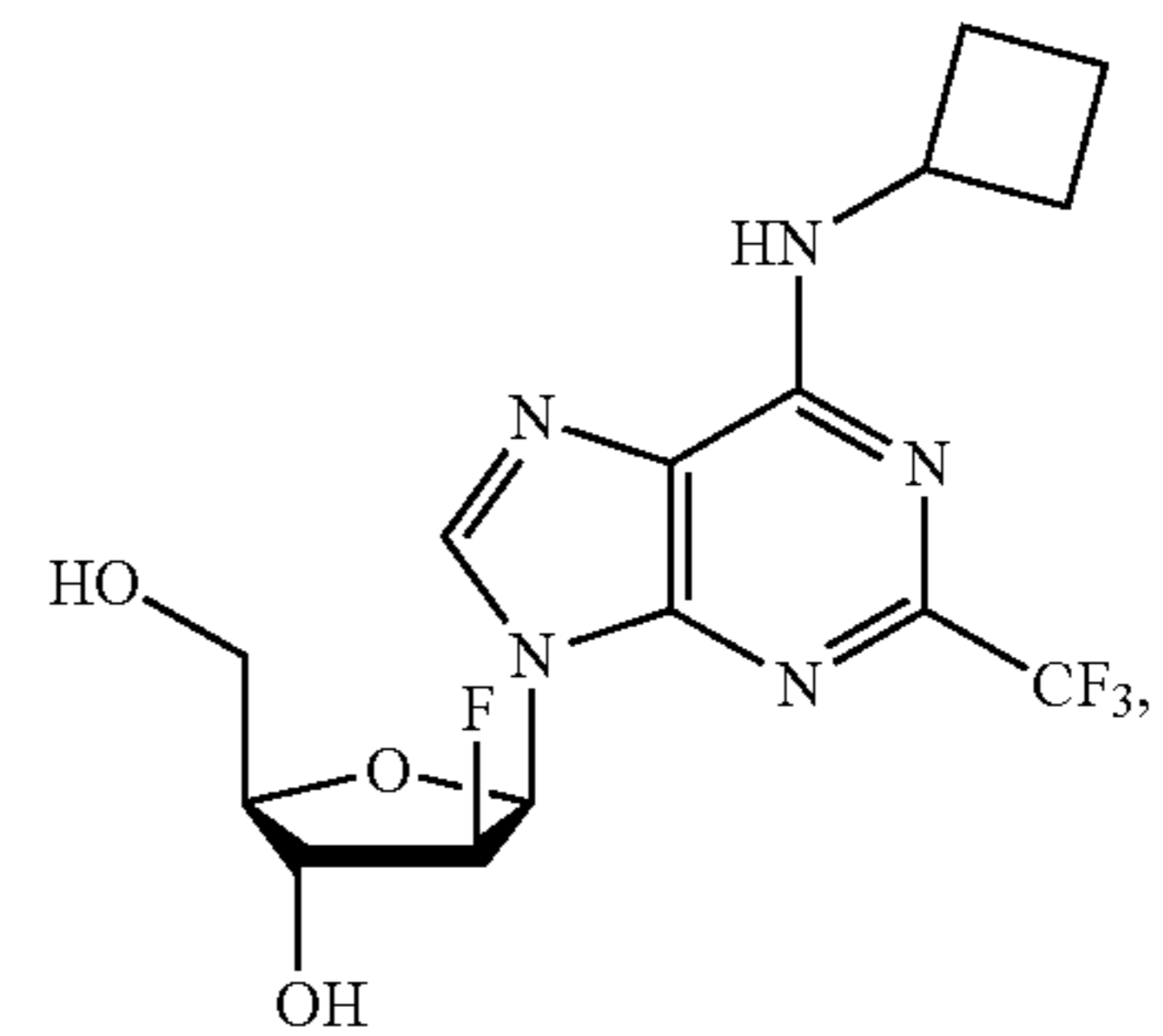
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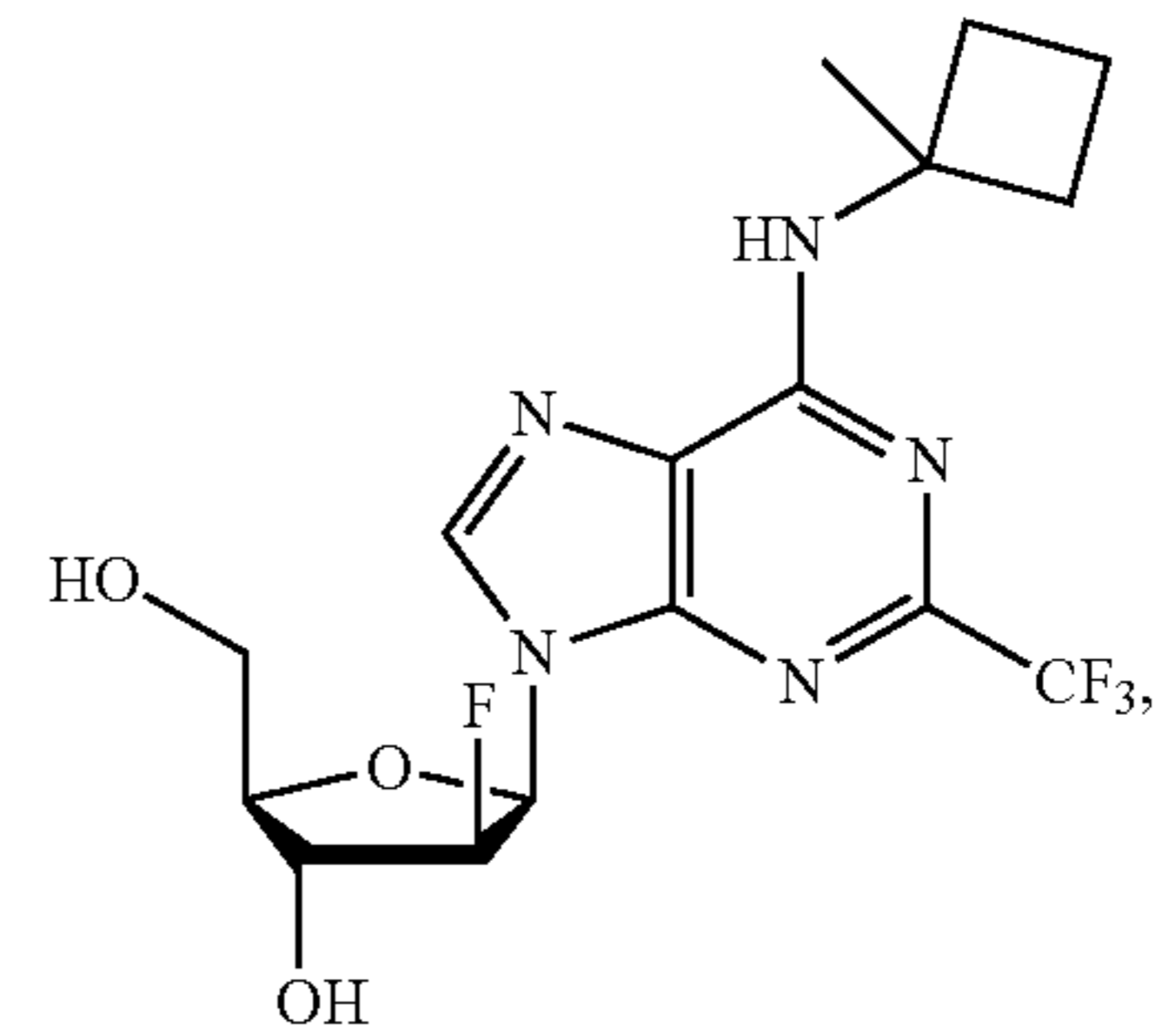
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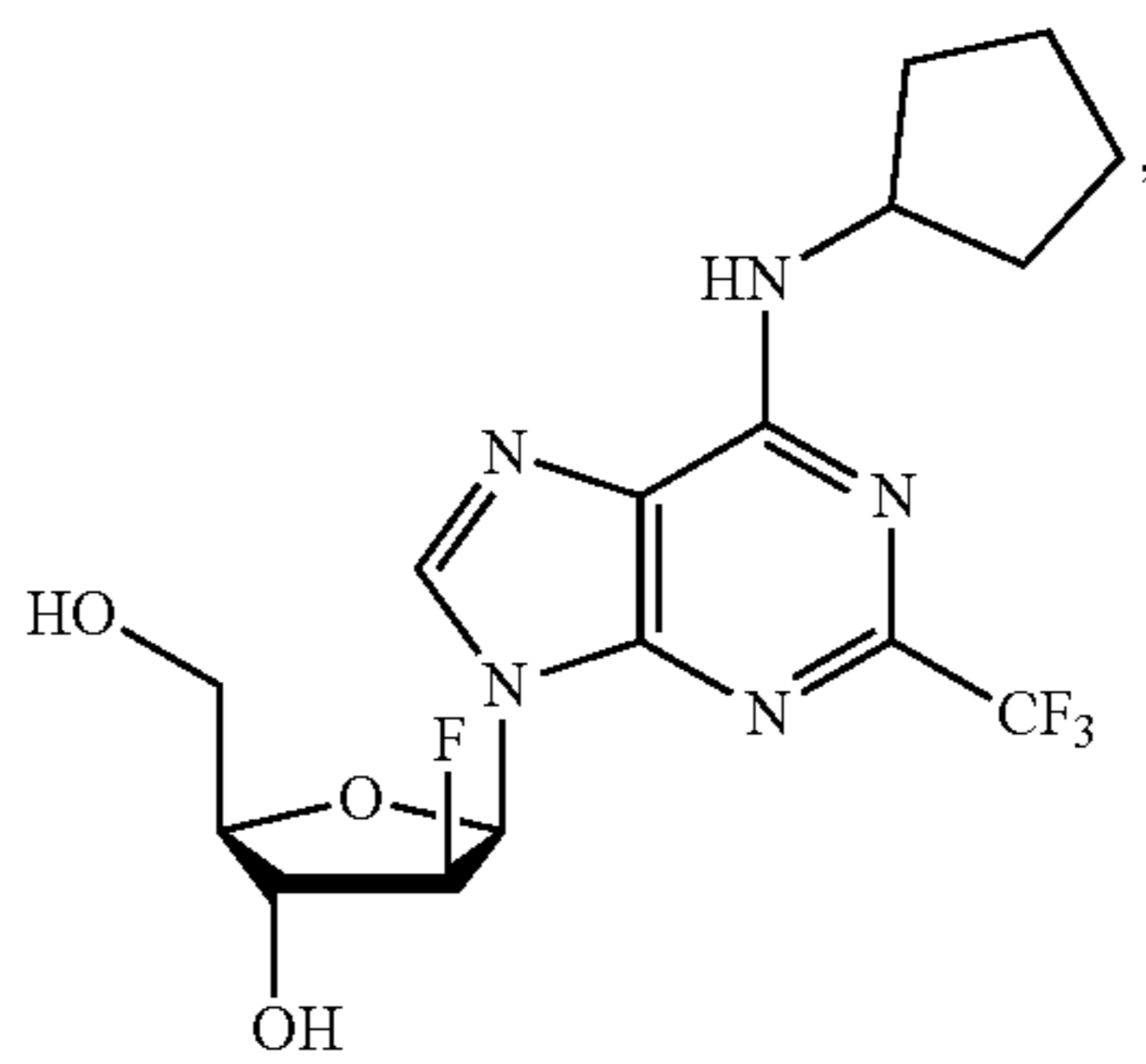
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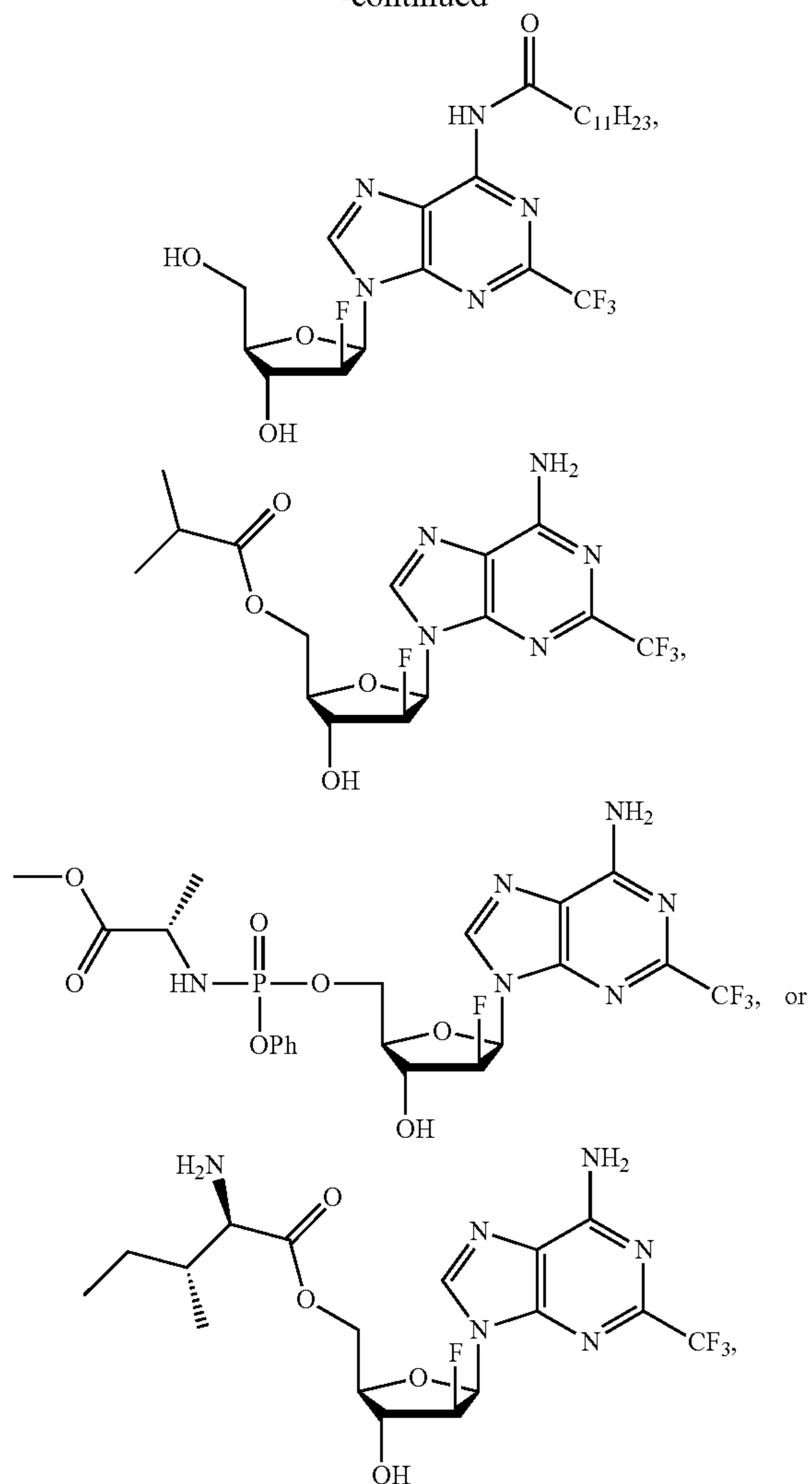


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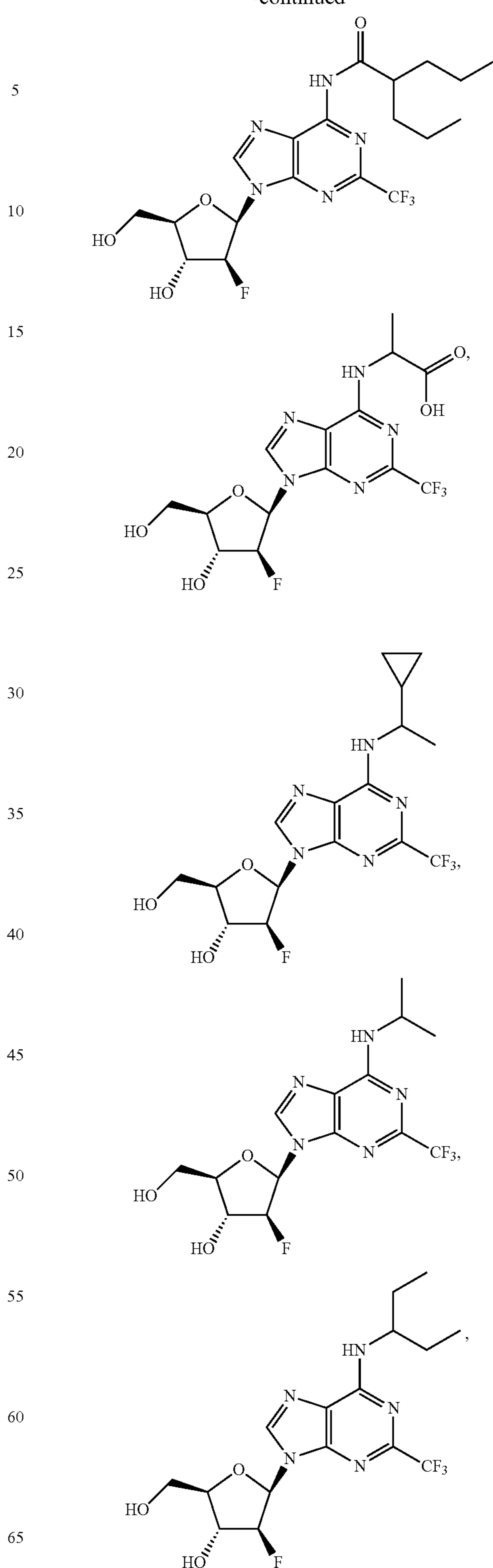
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82

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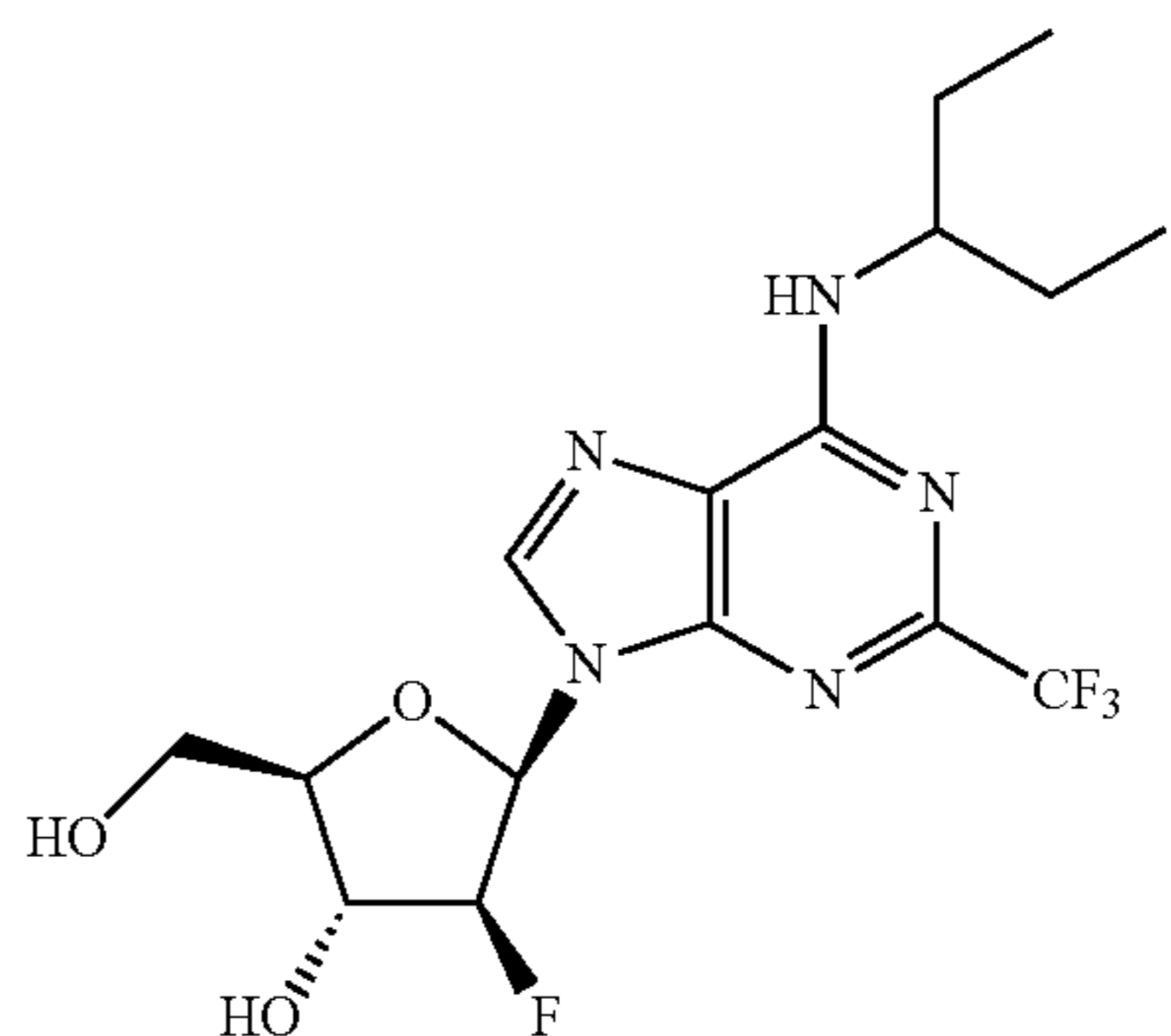
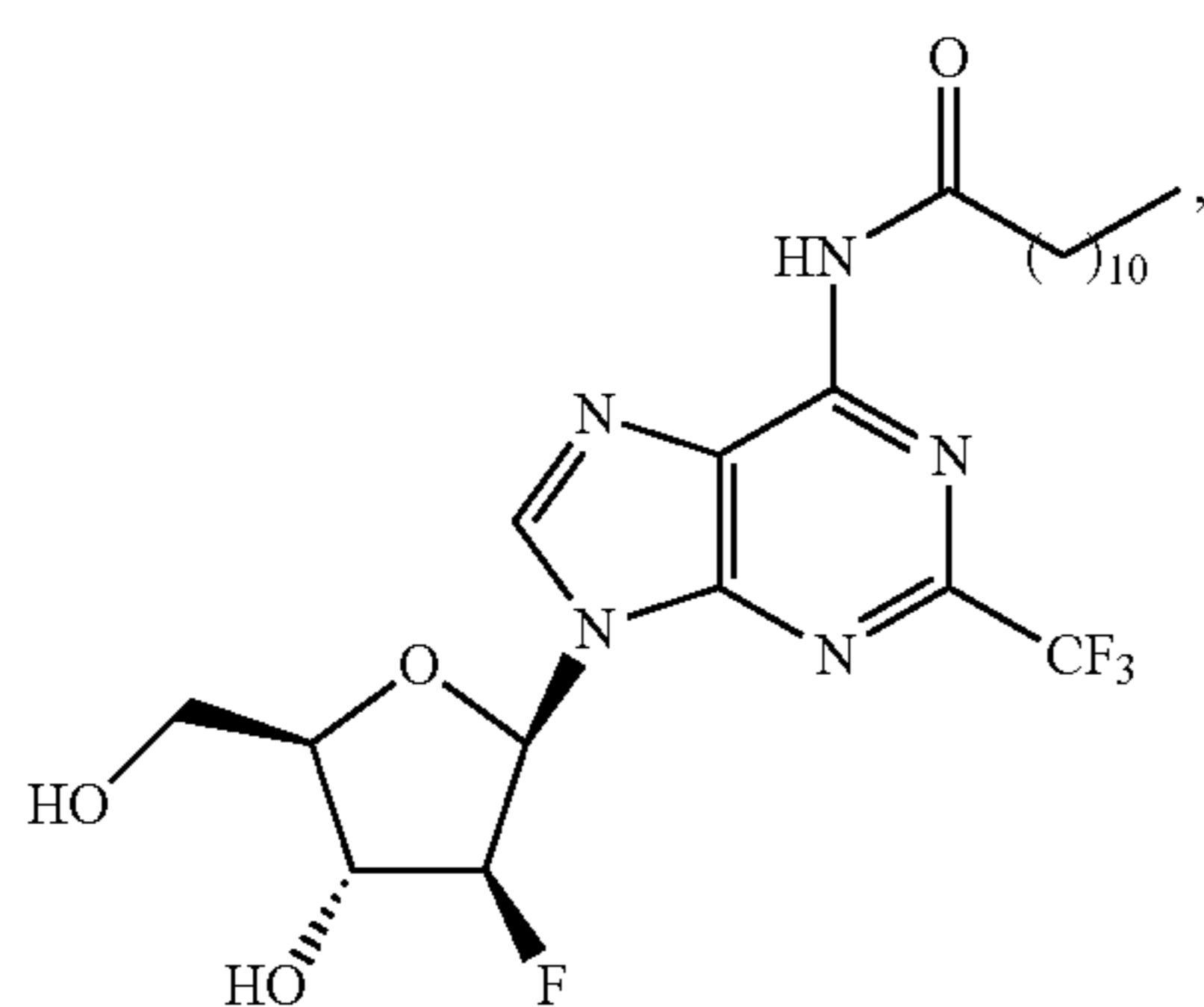


or a pharmaceutically acceptable salt thereof.

3. Prophetic Compounds

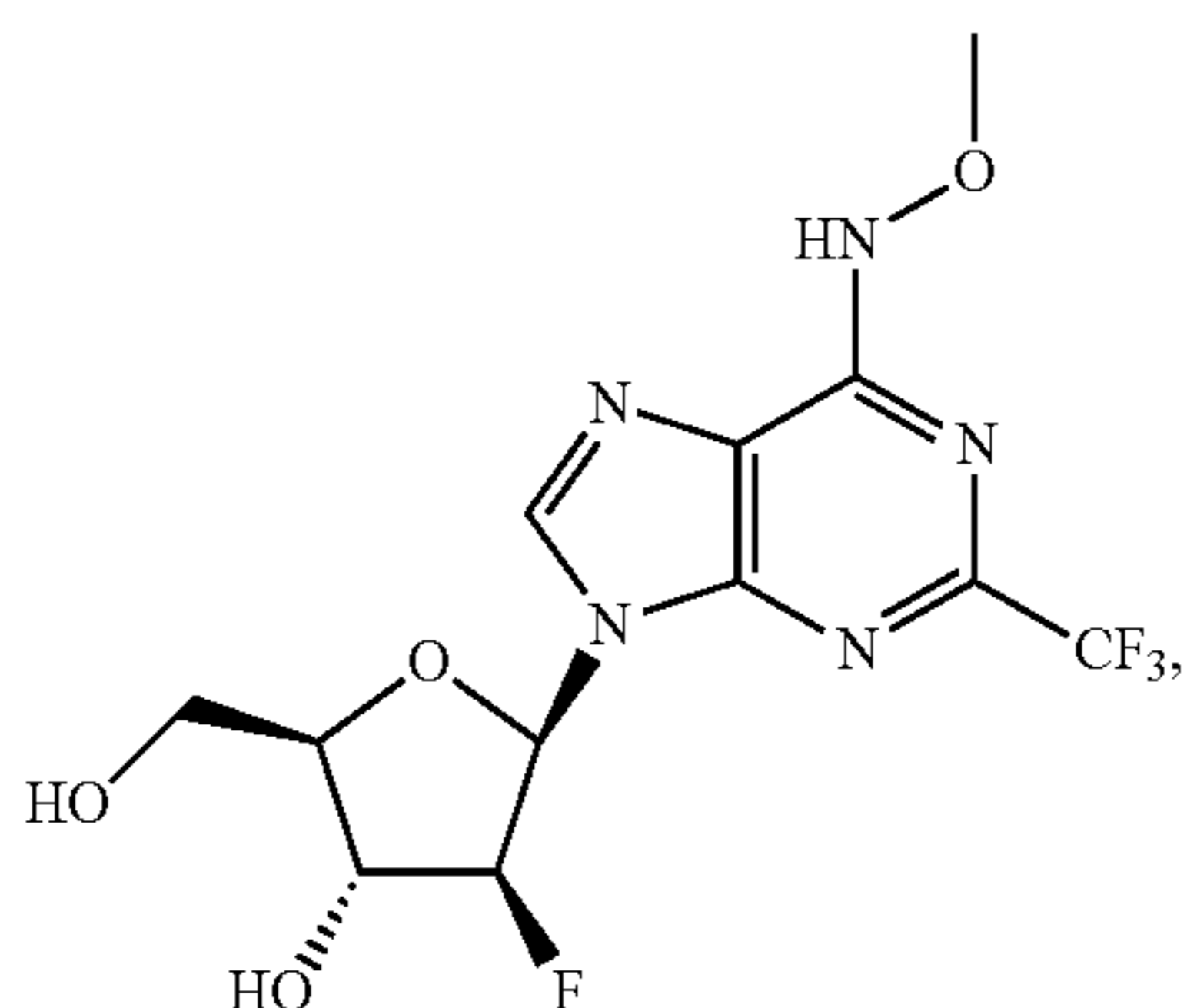
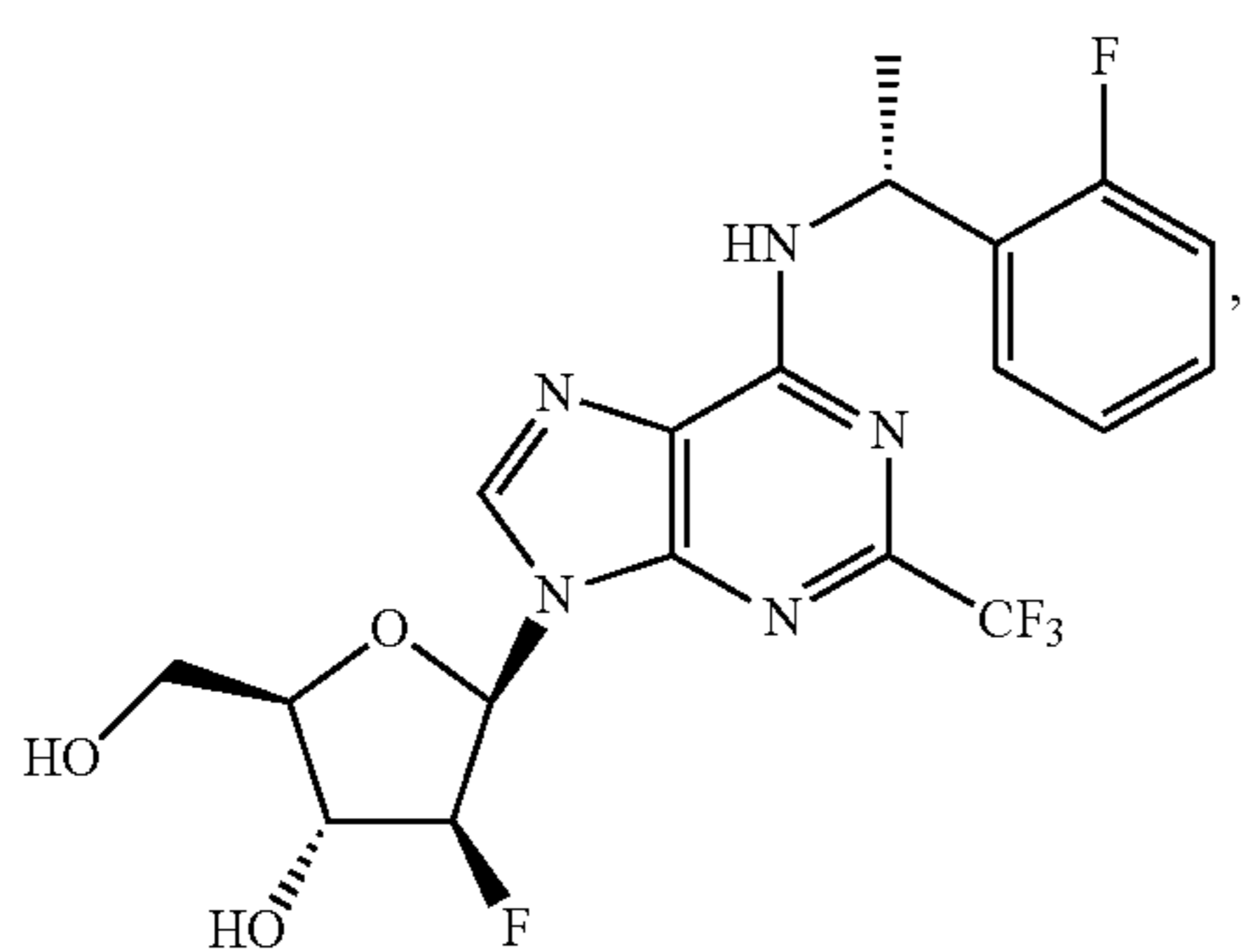
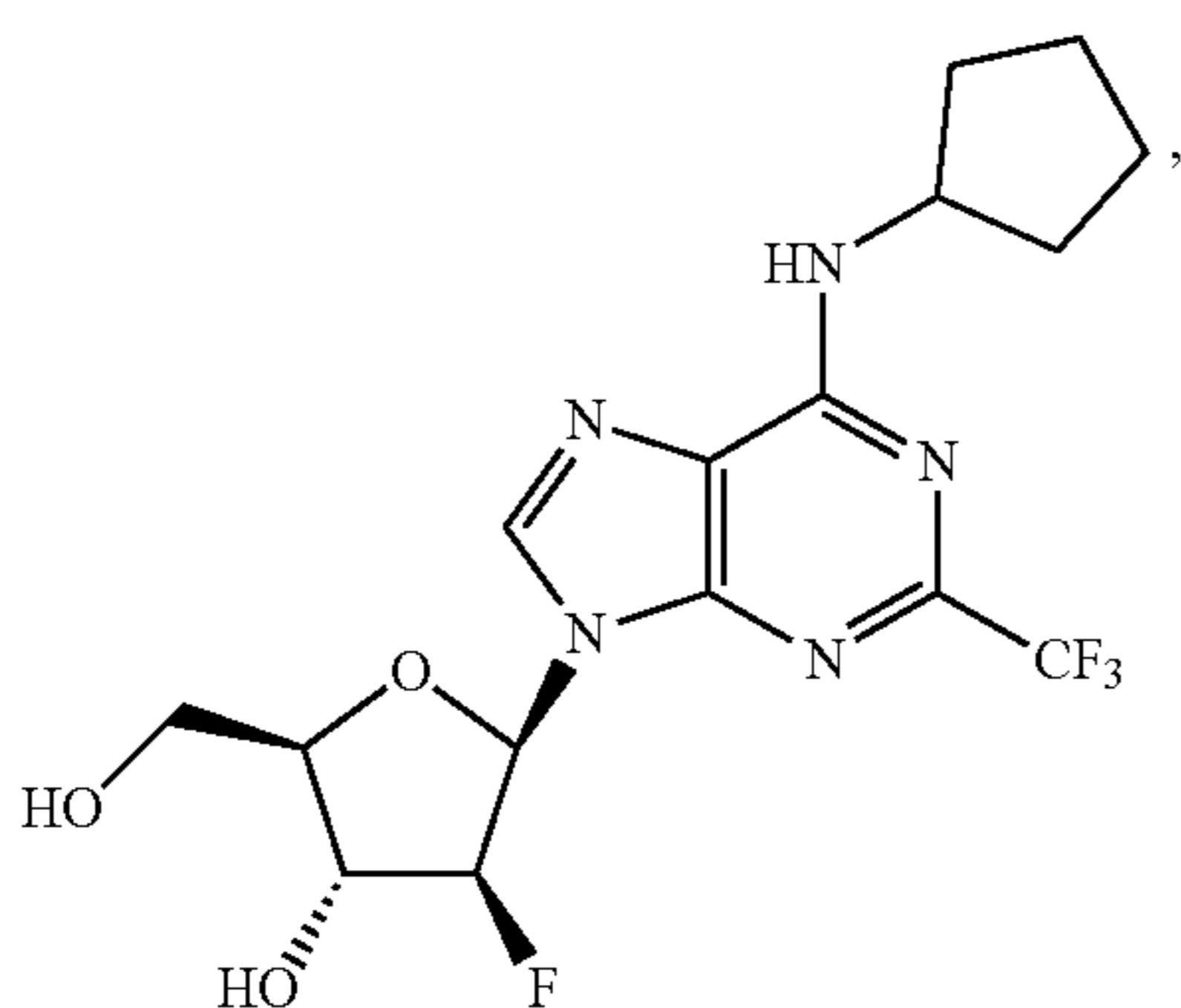
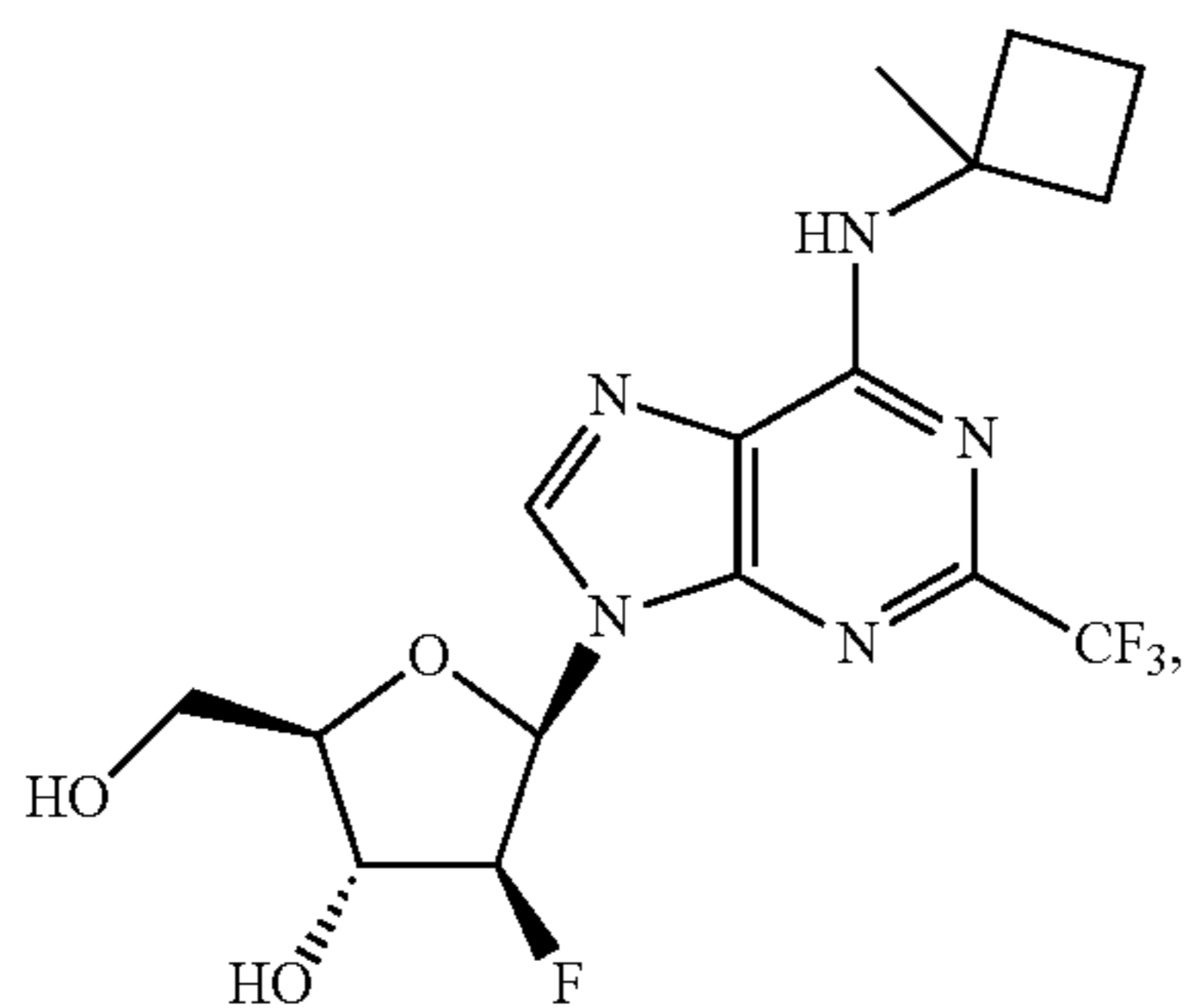
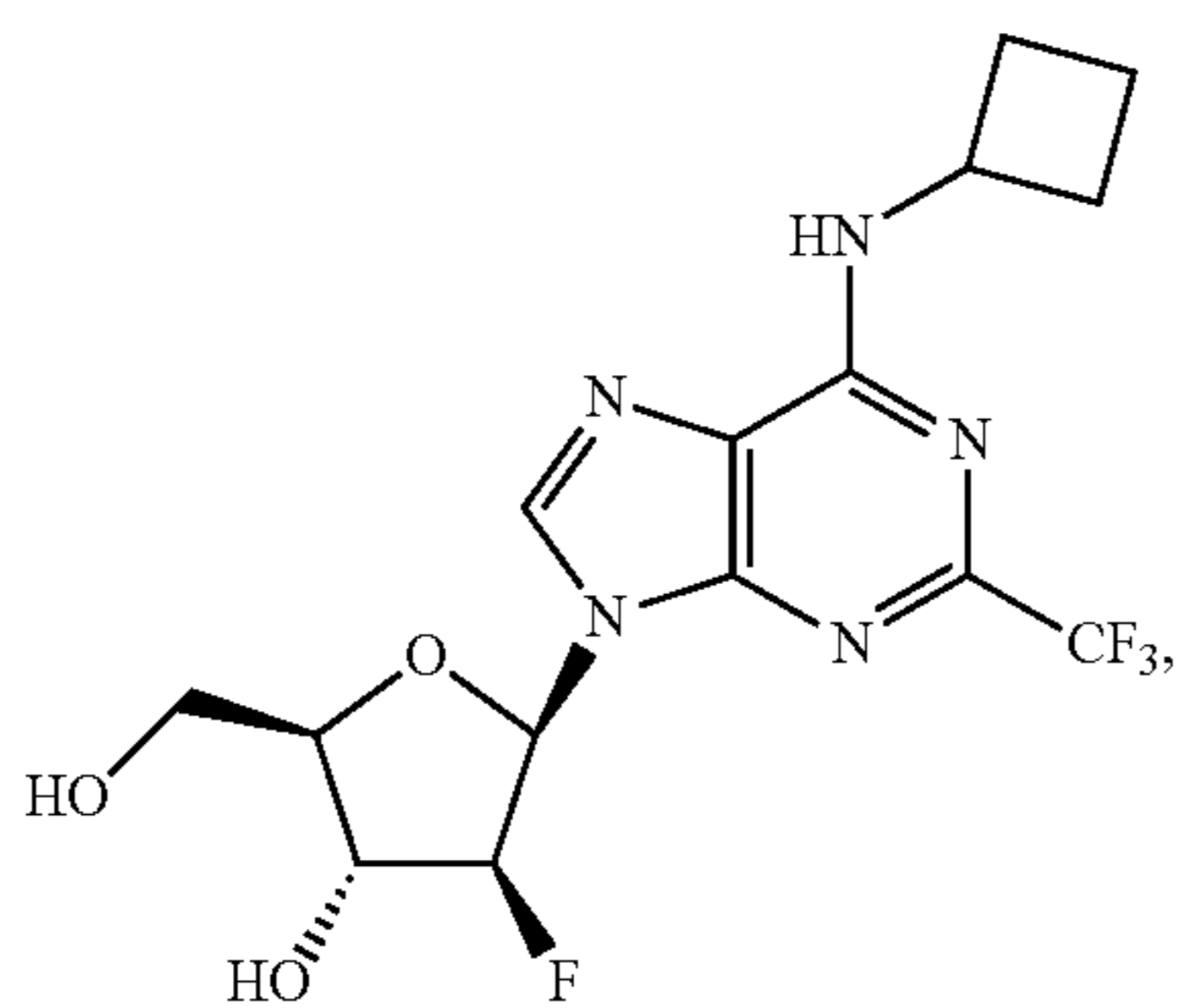
The following compound examples are prophetic, and can be prepared using the synthesis methods described herein above and other general methods as needed as would be known to one skilled in the art. It is anticipated that the prophetic compounds would be useful for the treatment of disorders of uncontrolled cellular proliferation such as, for example, cancer, and such utility can be determined using the assay methods described herein below.

In one aspect, a compound can be selected from:



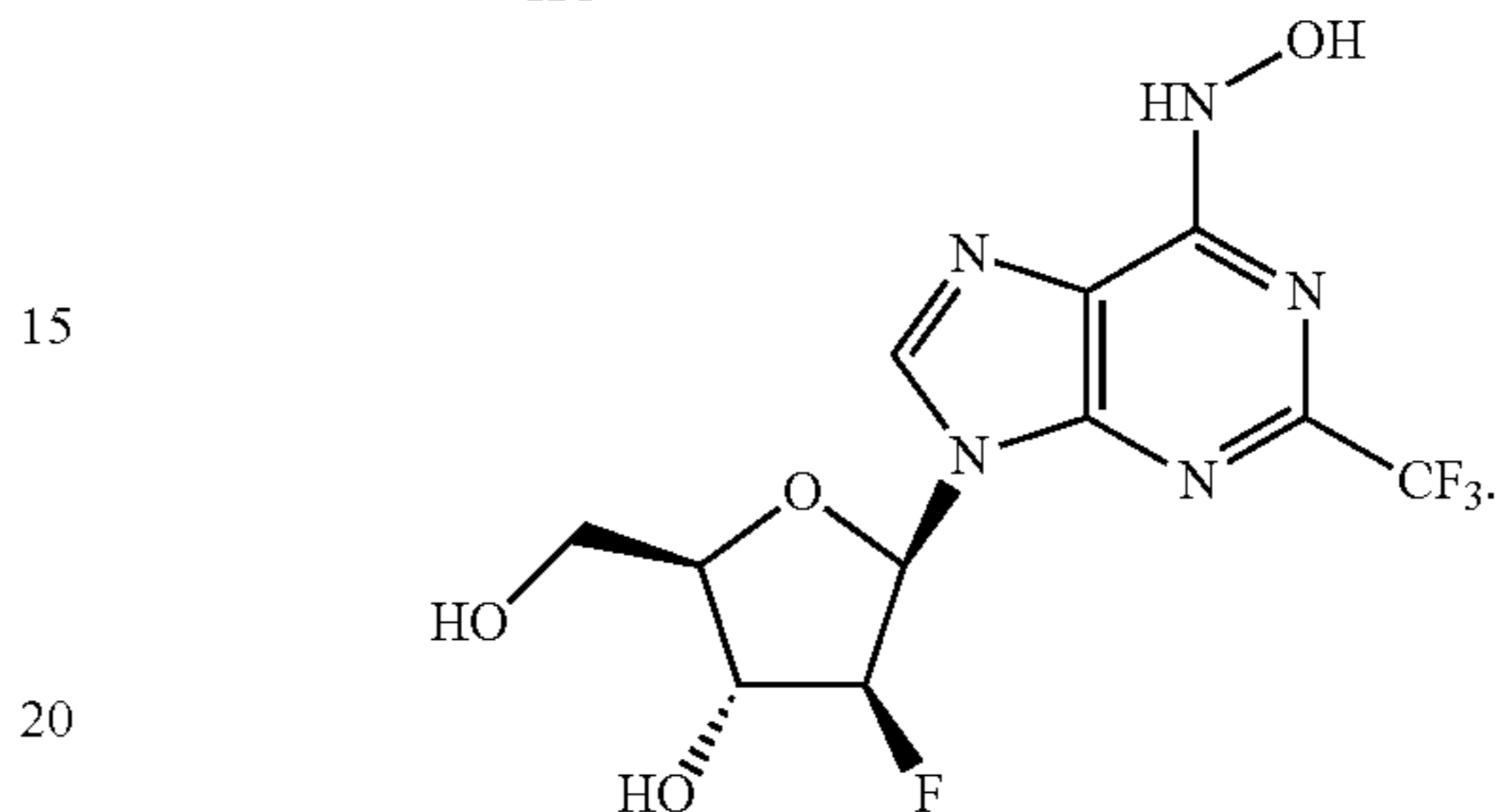
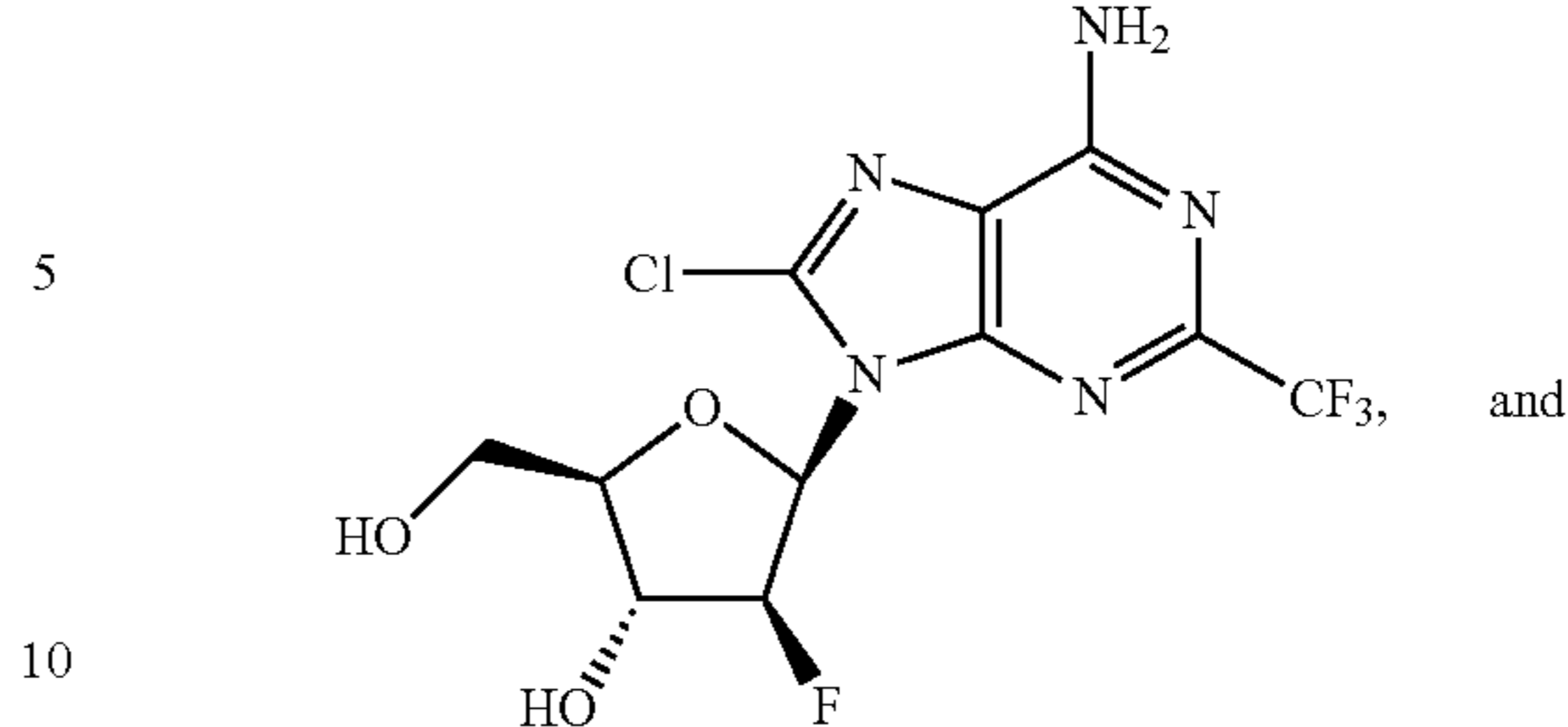
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It is contemplated that one or more compounds can optionally be omitted from the disclosed invention.

It is understood that the disclosed compounds can be used in connection with the disclosed methods, compositions, kits, and uses.

It is understood that pharmaceutical acceptable derivatives of the disclosed compounds can be used also in connection with the disclosed methods, compositions, kits, and uses. The pharmaceutical acceptable derivatives of the compounds can include any suitable derivative, such as pharmaceutically acceptable salts as discussed below, isomers, radiolabeled analogs, tautomers, and the like.

C. Methods of Making a Compound

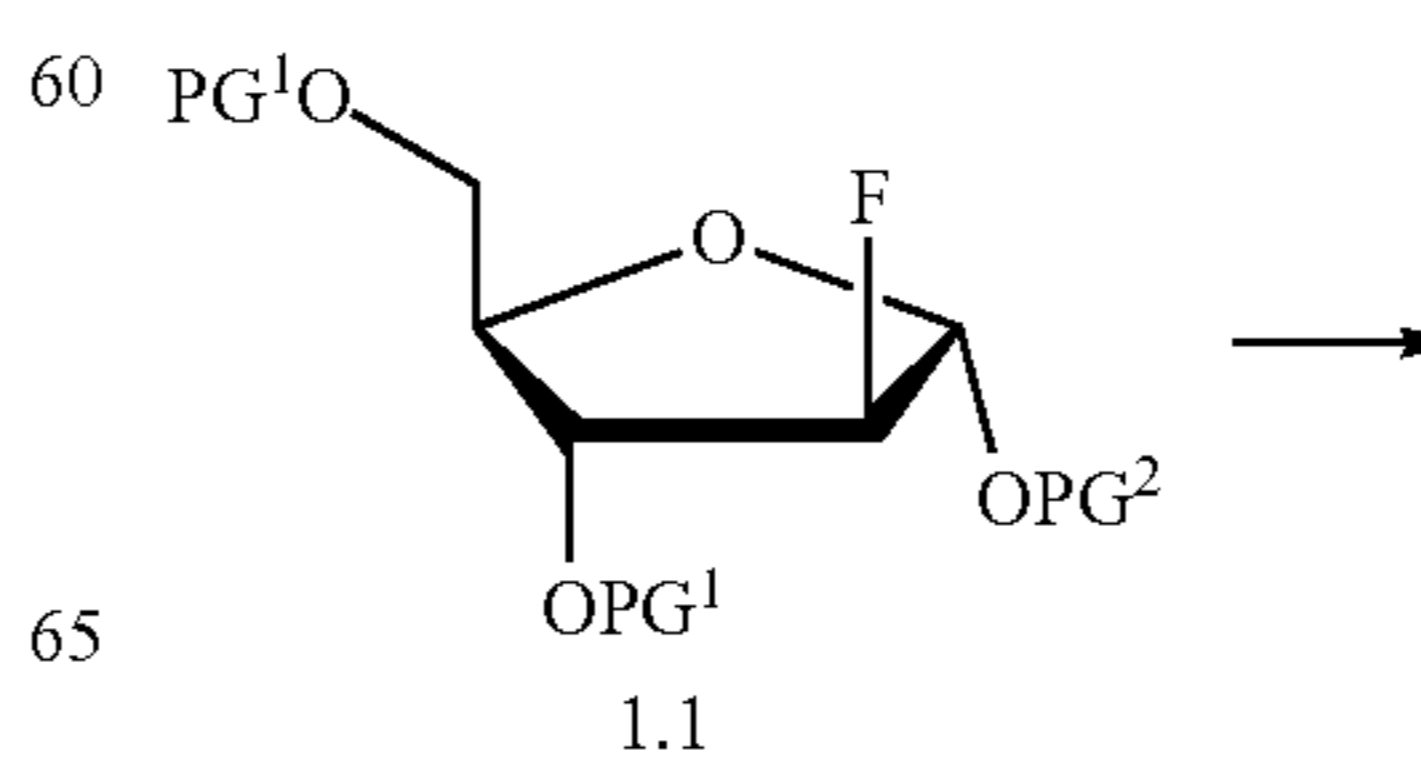
The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, as described and exemplified below. In certain specific examples, the disclosed compounds can be prepared by Routes I-V, as described and exemplified below. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

1. Route I

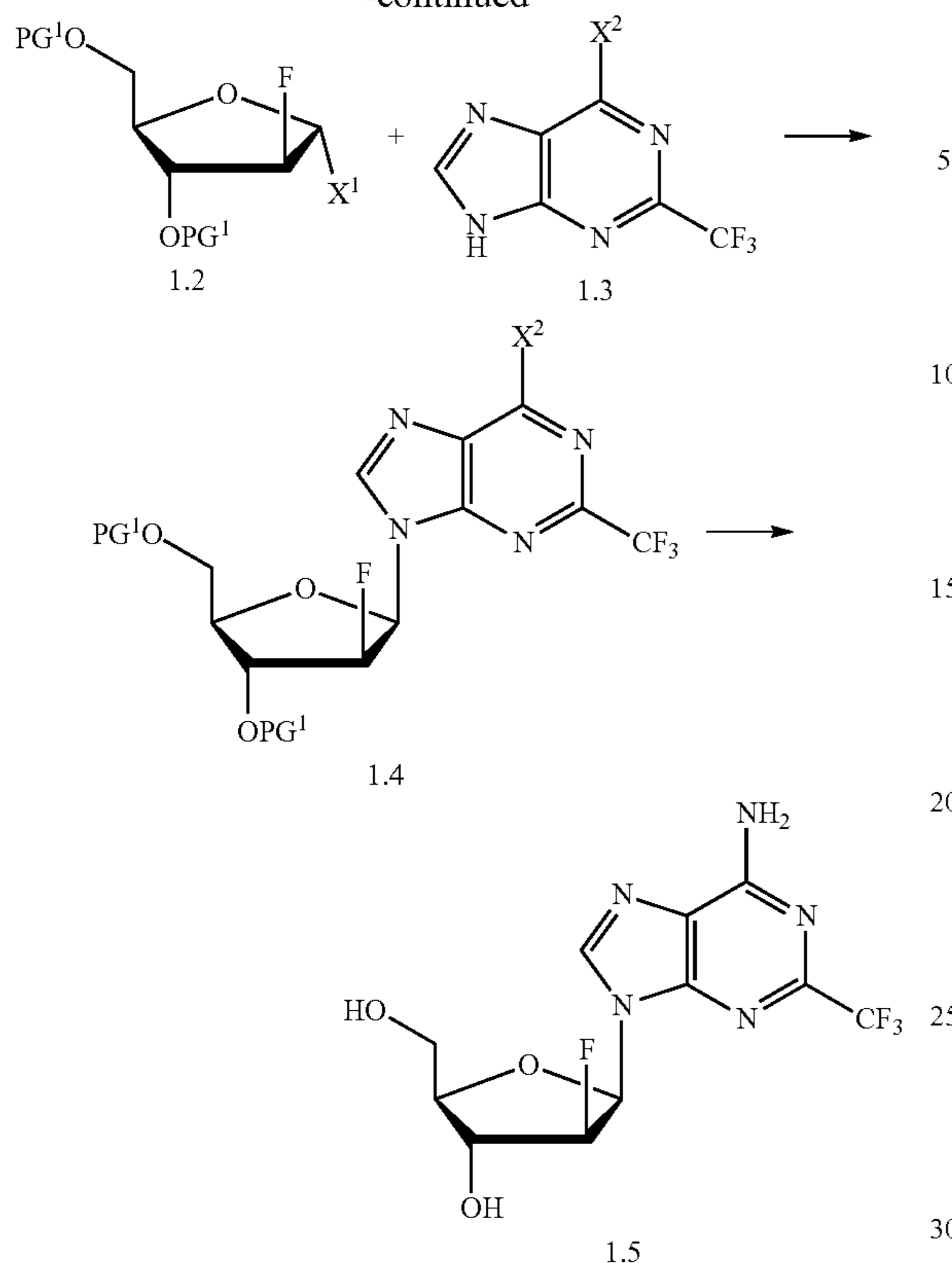
In one aspect, a disclosed nucleoside can be prepared as shown below.

SCHEME 1A.



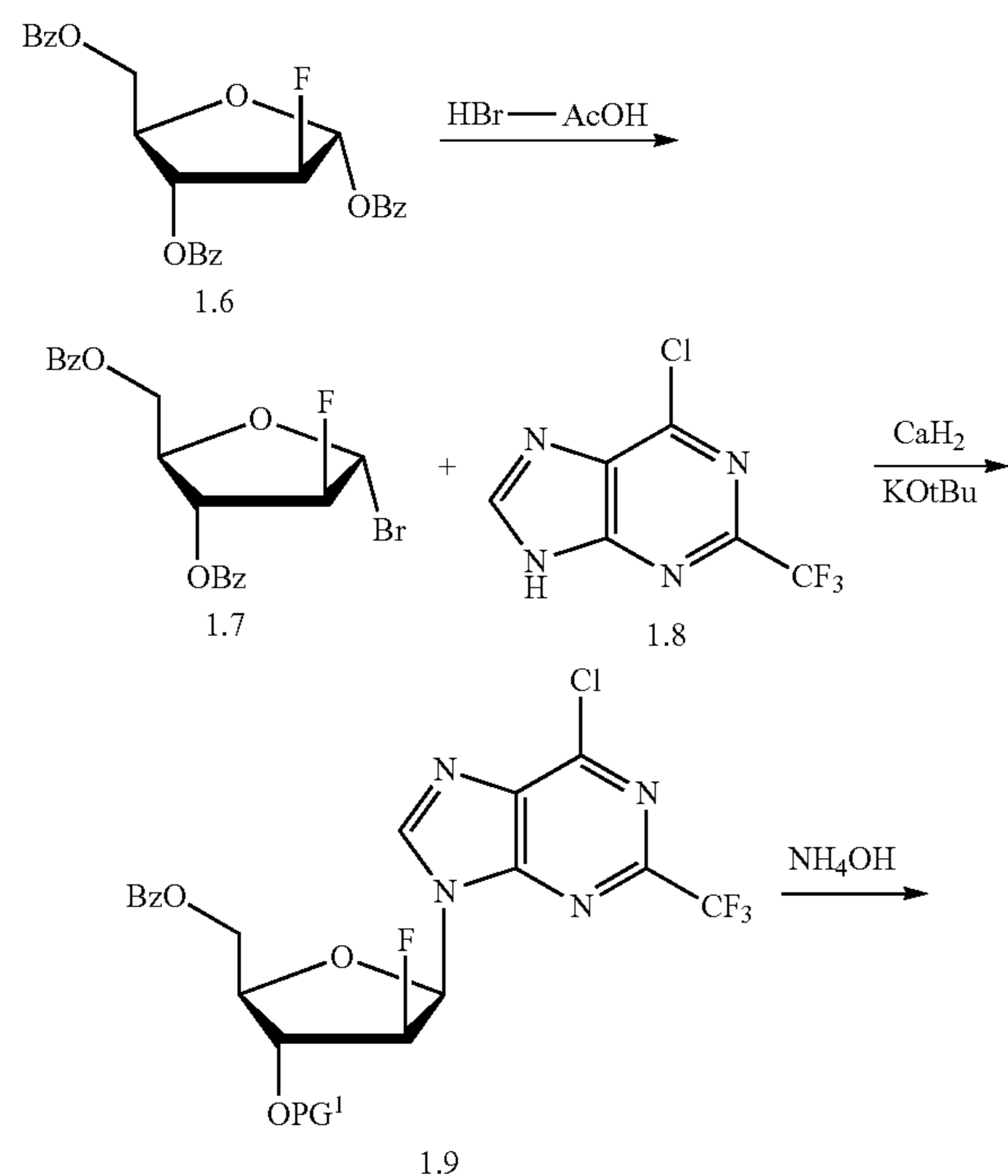
85

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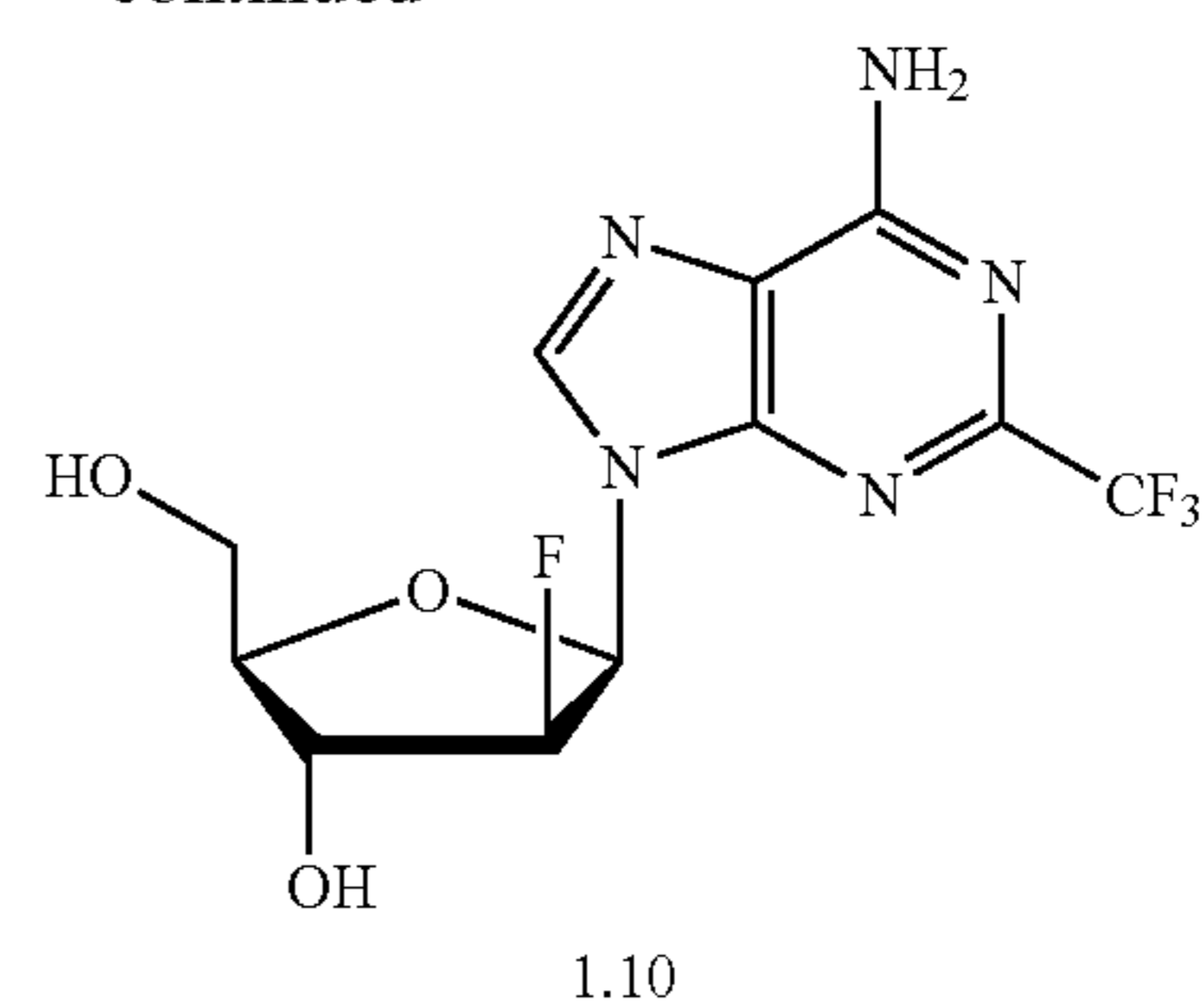
Compounds are represented in generic form, wherein each of PG¹ and PG² is independently an alcohol protecting group, wherein each of X¹ and X² is independently halogen, and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 1B.



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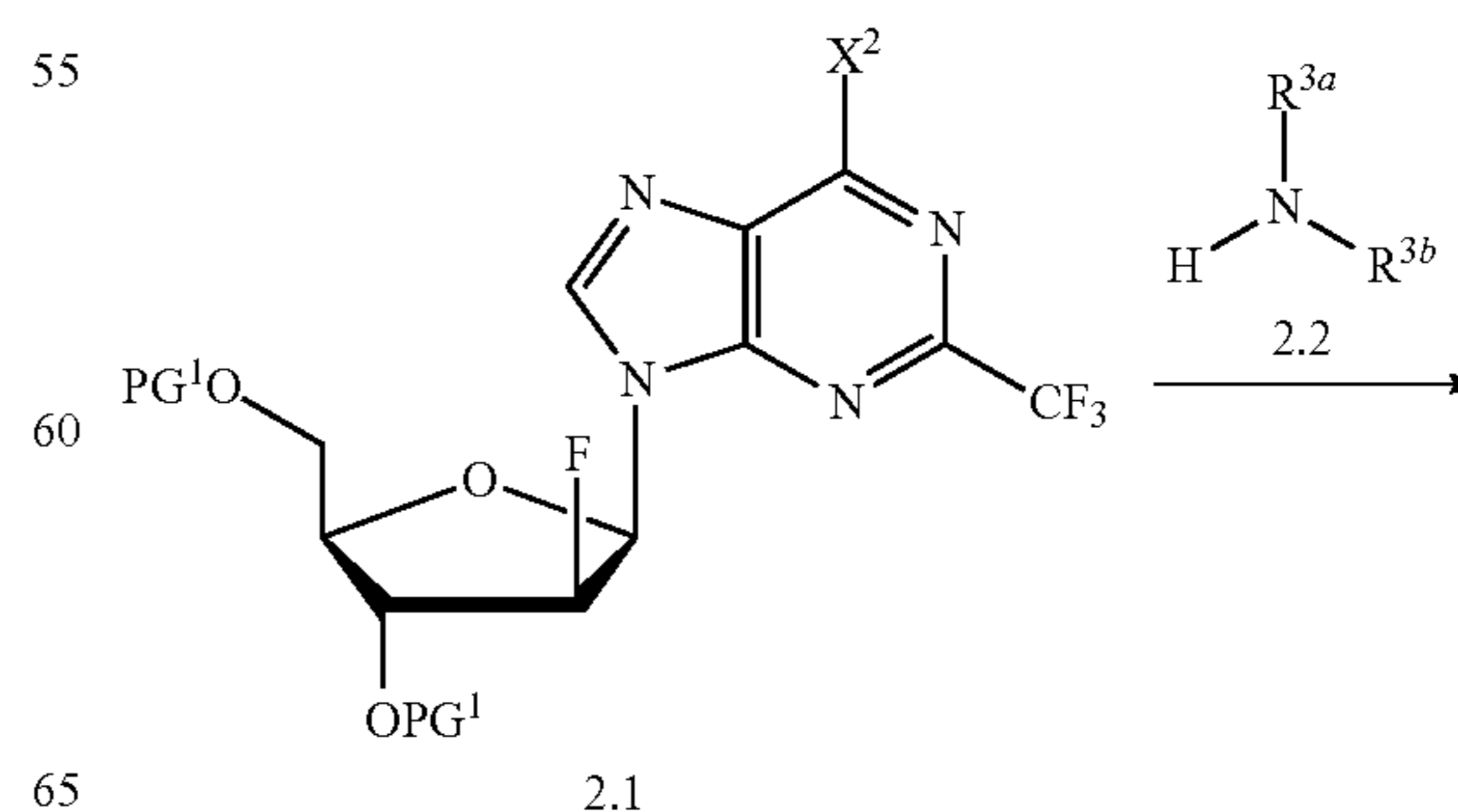


In one aspect, compounds of type 1.10, and similar compounds, can be prepared according to reaction Scheme 1B above. Thus, compounds of type 1.7 can be prepared by a substitution reaction of an appropriate sugar, e.g., 1.6 as shown above. Appropriate sugars are commercially available or prepared by methods known to one skilled in the art. The substitution reaction is carried out in the presence of an appropriate halide source, e.g., hydrobromic acid solution in acetic acid as shown above. Compounds of type 1.9 can be prepared by a coupling reaction between of an appropriate halide, e.g., 1.7 as shown above, and an appropriate purine derivative, e.g., 1.8 as shown above. Appropriate purine derivatives are commercially available or prepared by methods known to one skilled in the art. The substitution reaction is carried out in the presence of an appropriate base, e.g., potassium tert-butoxide as shown above, and an appropriate desiccant, e.g., calcium hydride as shown above. Compounds of type 1.10 can be prepared by displacement and deprotection of an appropriate nucleoside, e.g., 1.9 as shown above. The reaction is carried out in the presence of an appropriate nucleophile/base, e.g., ammonium hydroxide as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 1.1, 1.2, 1.3, and 1.4), can be substituted in the reaction to provide substituted nucleoside derivatives similar to Formula 1.5.

2. Route II

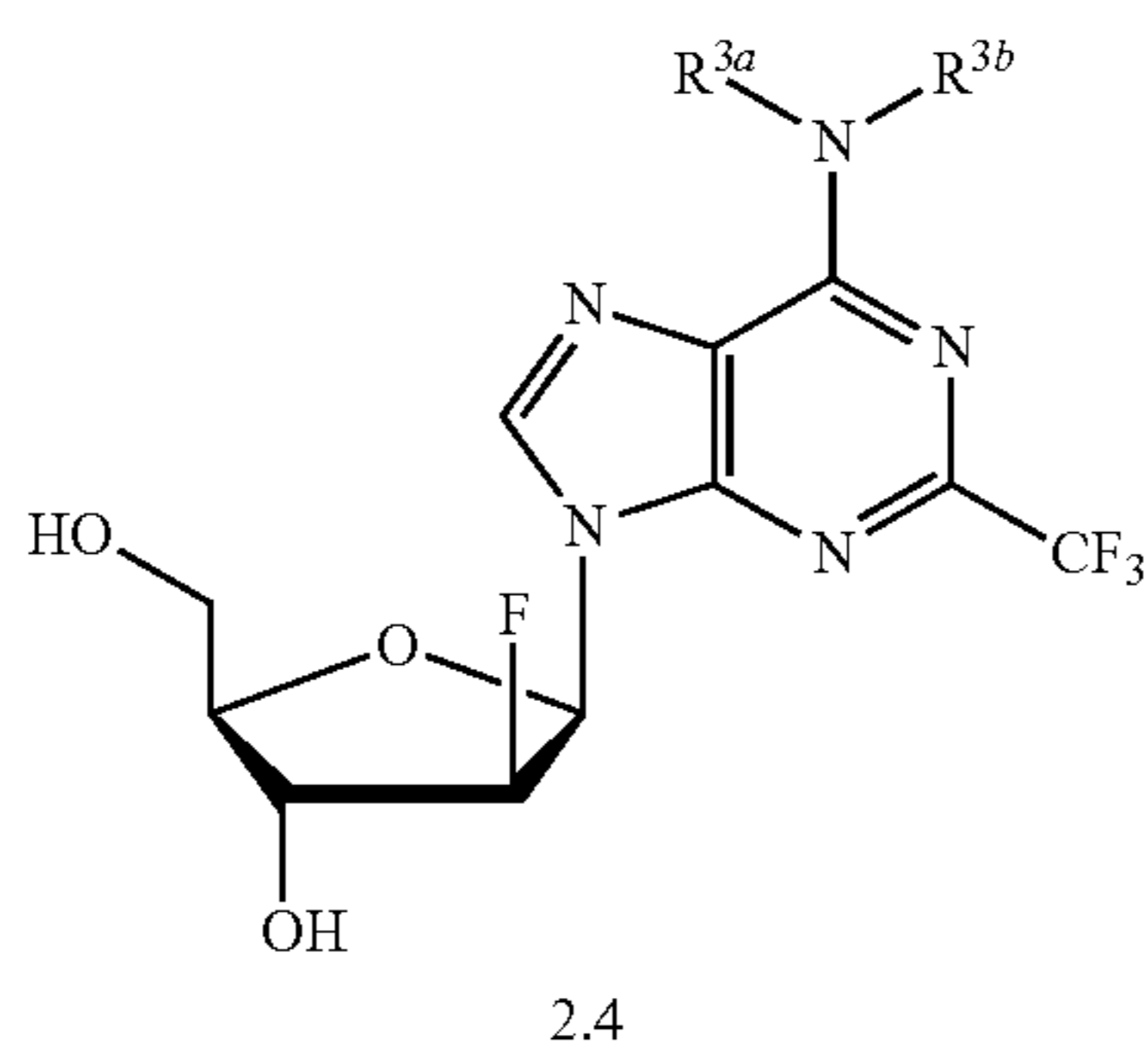
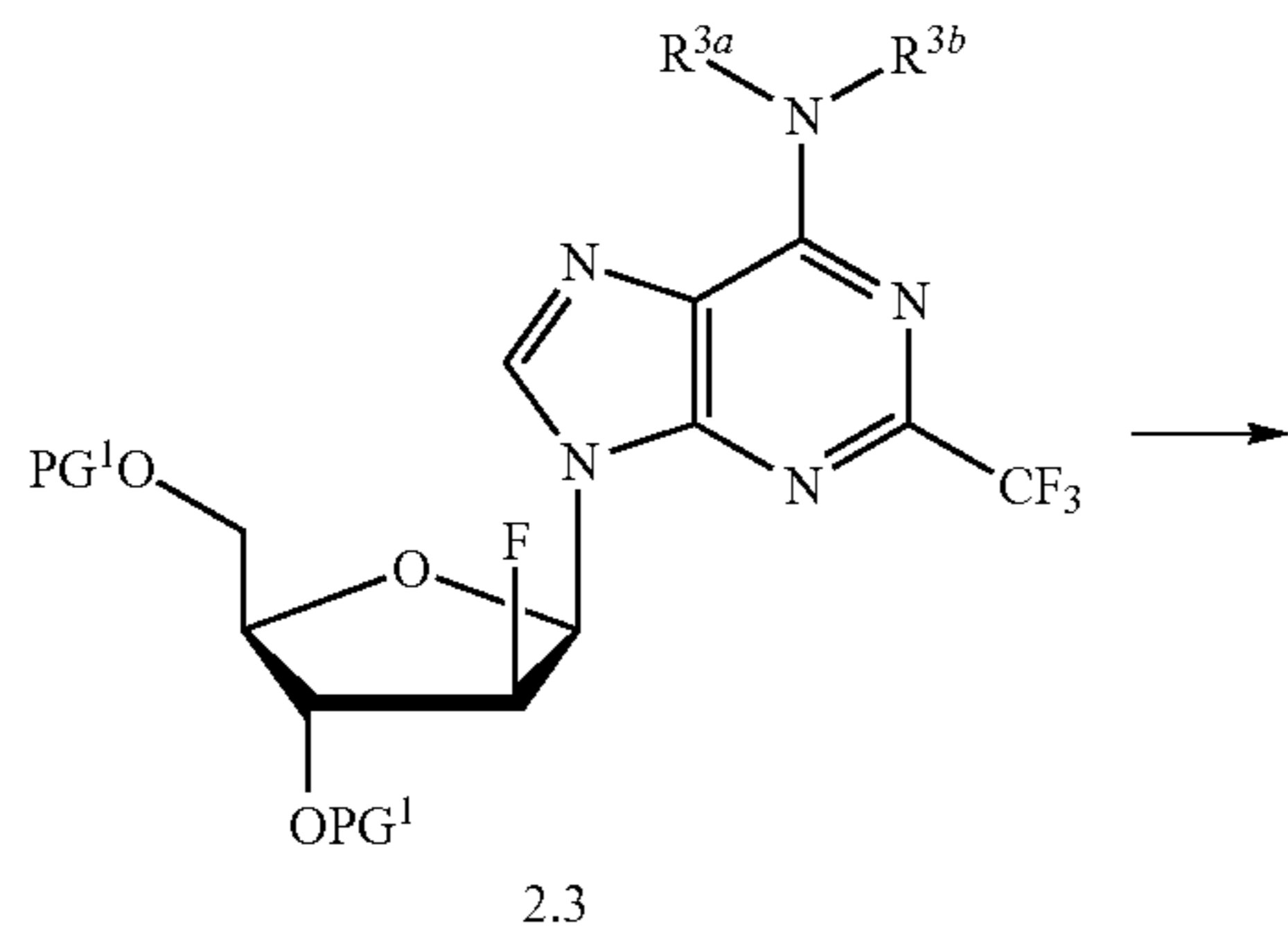
In one aspect, a disclosed nucleoside can be prepared as shown below.

SCHEME 2A.



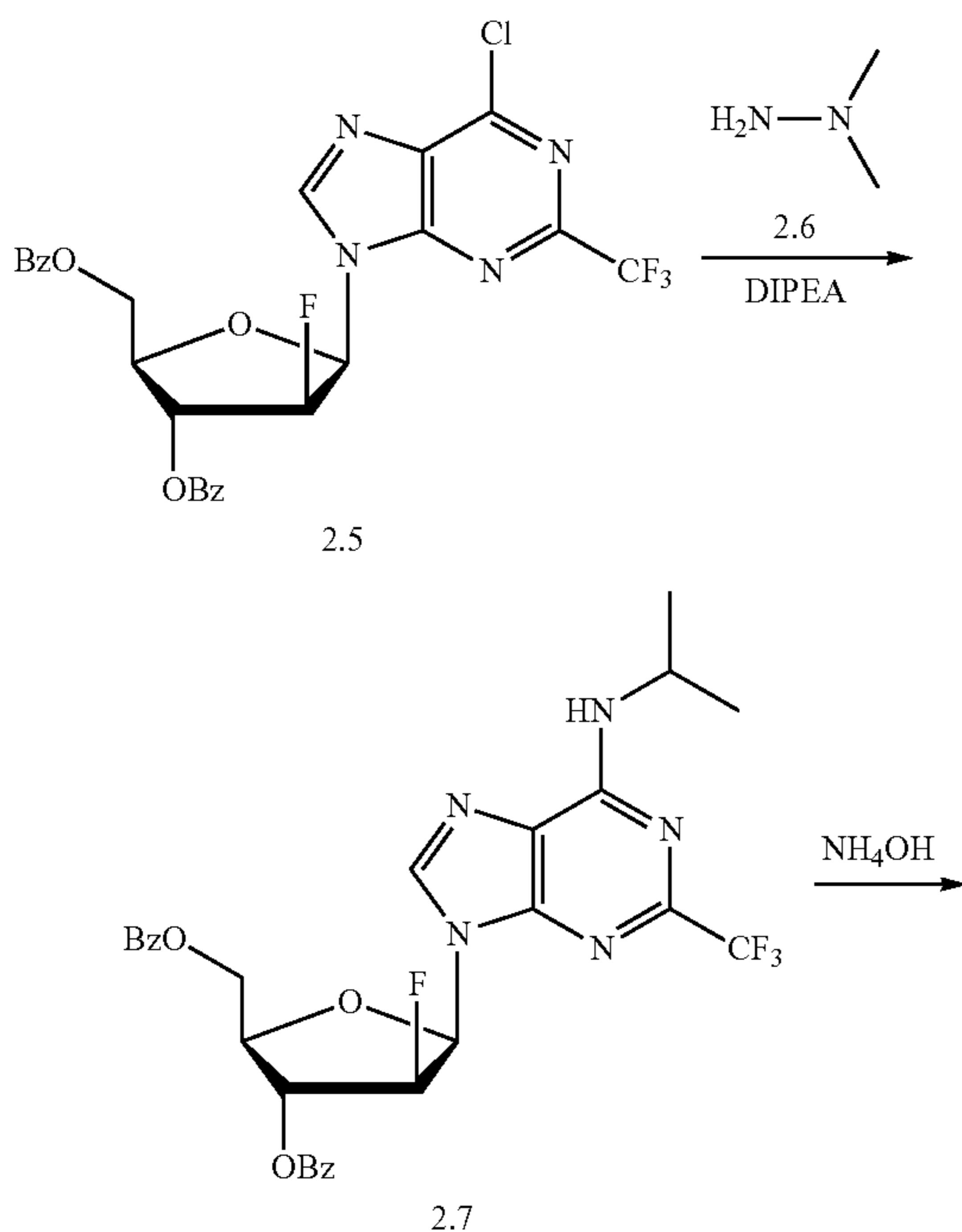
87

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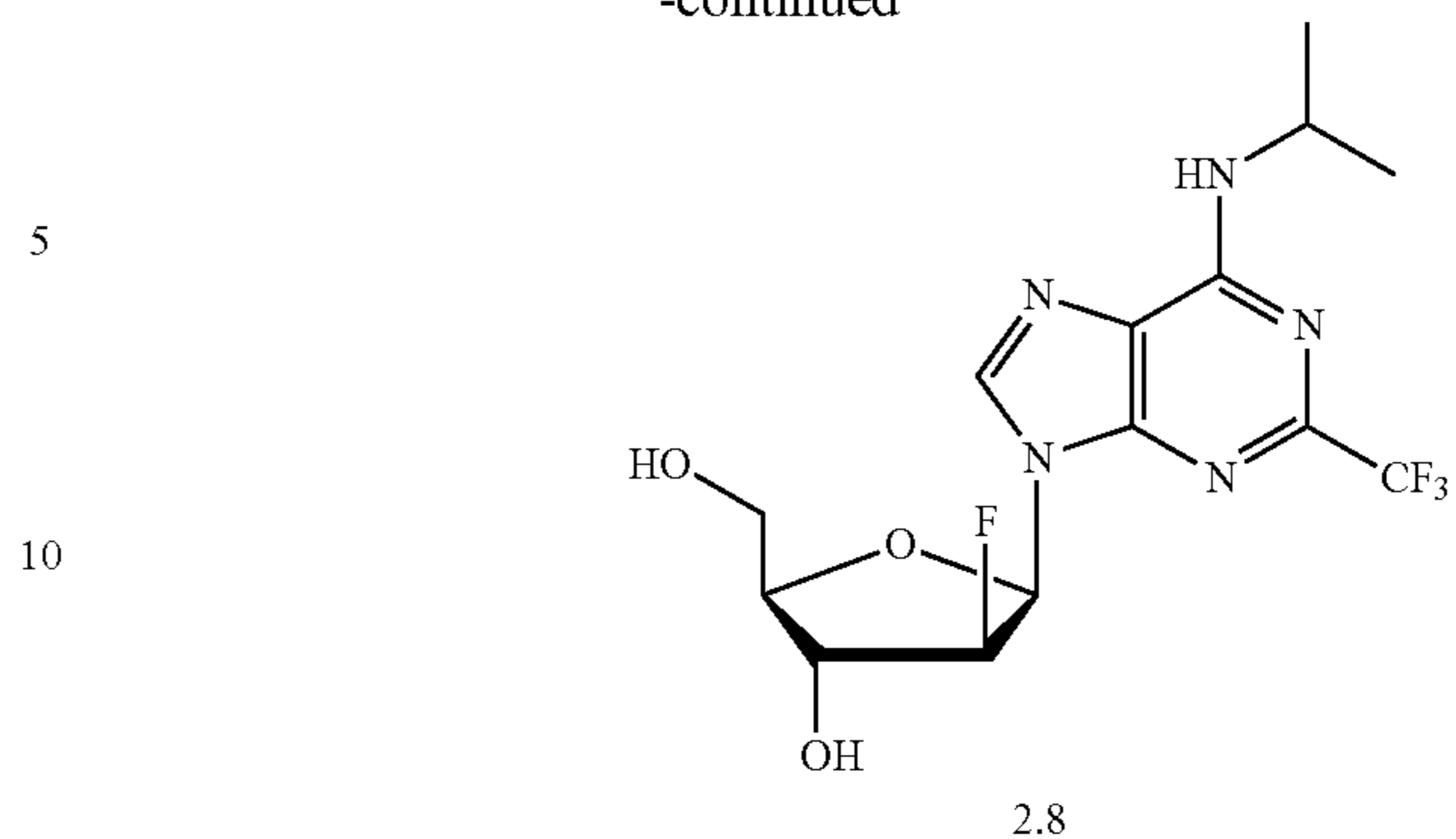
Compounds are represented in generic form, wherein PG^1 is an alcohol protecting group, wherein X^2 is halogen, and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 2B.



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-continued



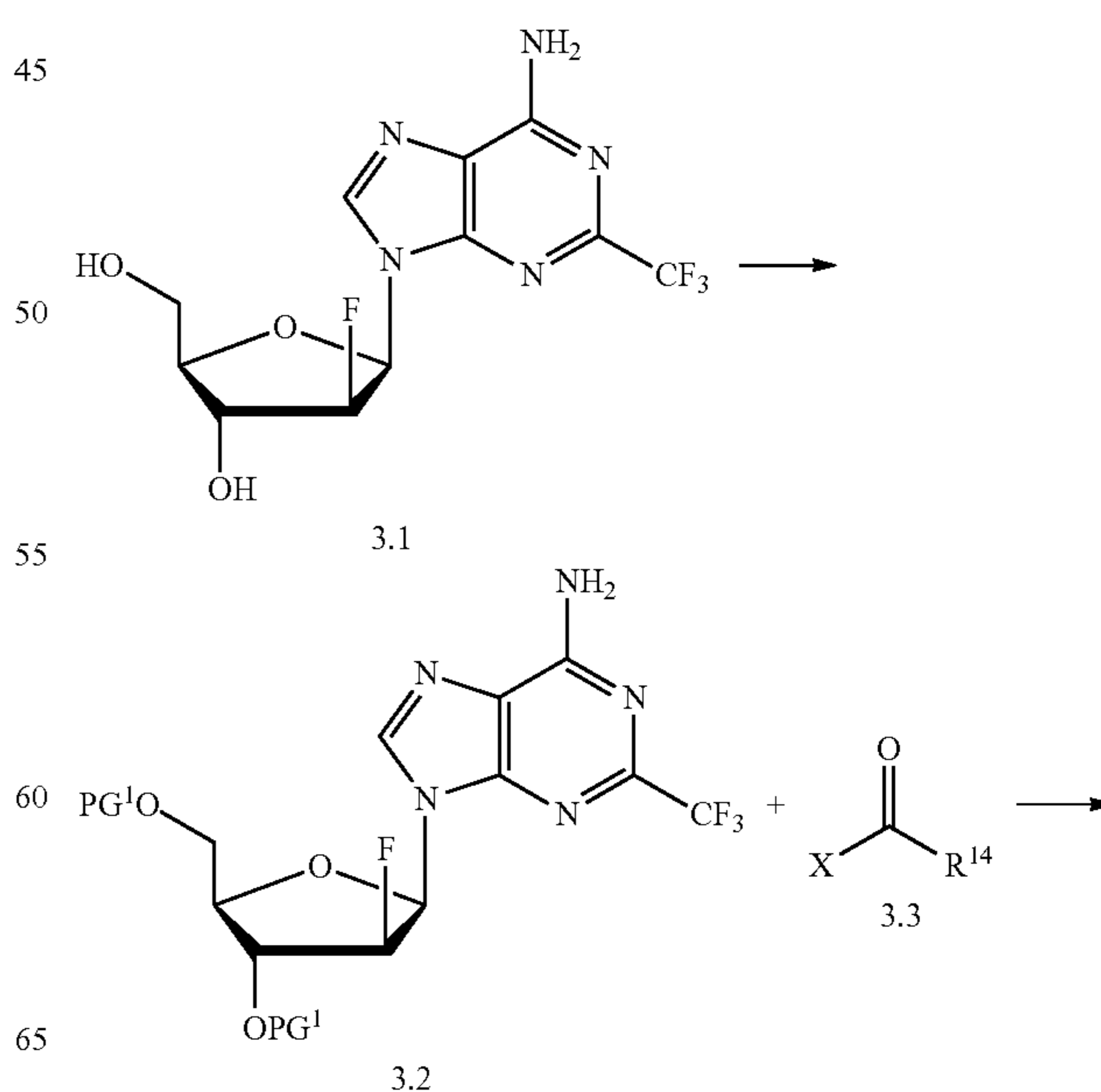
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In one aspect, compounds of type 2.8, and similar compounds, can be prepared according to reaction Scheme 2B above. Thus, compounds of type 2.7 can be prepared by a coupling reaction between an appropriate halide, e.g., 2.5 as shown above, and an appropriate amine, e.g., 2.6 as shown above. Appropriate halides and appropriate amines are commercially available or prepared by methods known to one skilled in the art. The coupling reaction is carried out in the presence of an appropriate base, e.g., *N,N*-diisopropylethylamine (DIPEA) as shown above. Compounds of type 2.8 can be prepared by deprotection of an appropriate nucleoside, e.g., 2.7 as shown above. The deprotection reaction is carried out in the presence of an appropriate base, e.g., ammonium hydroxide as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 2.1, 2.2, and 2.3), can be substituted in the reaction to provide substituted nucleoside derivatives similar to Formula 2.4.

3. Route III

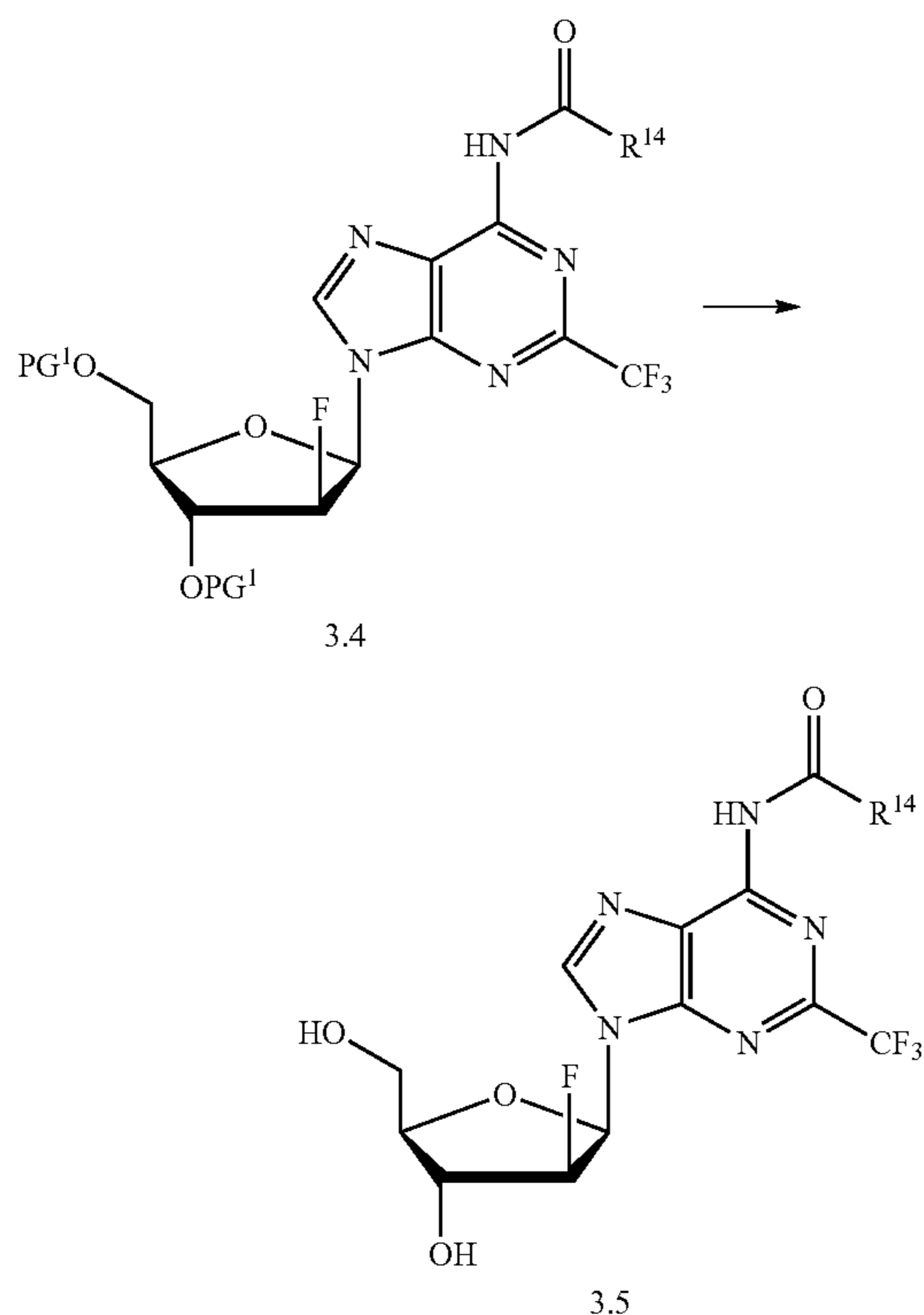
In one aspect, a disclosed nucleoside can be prepared as shown below.

SCHEME 3A.



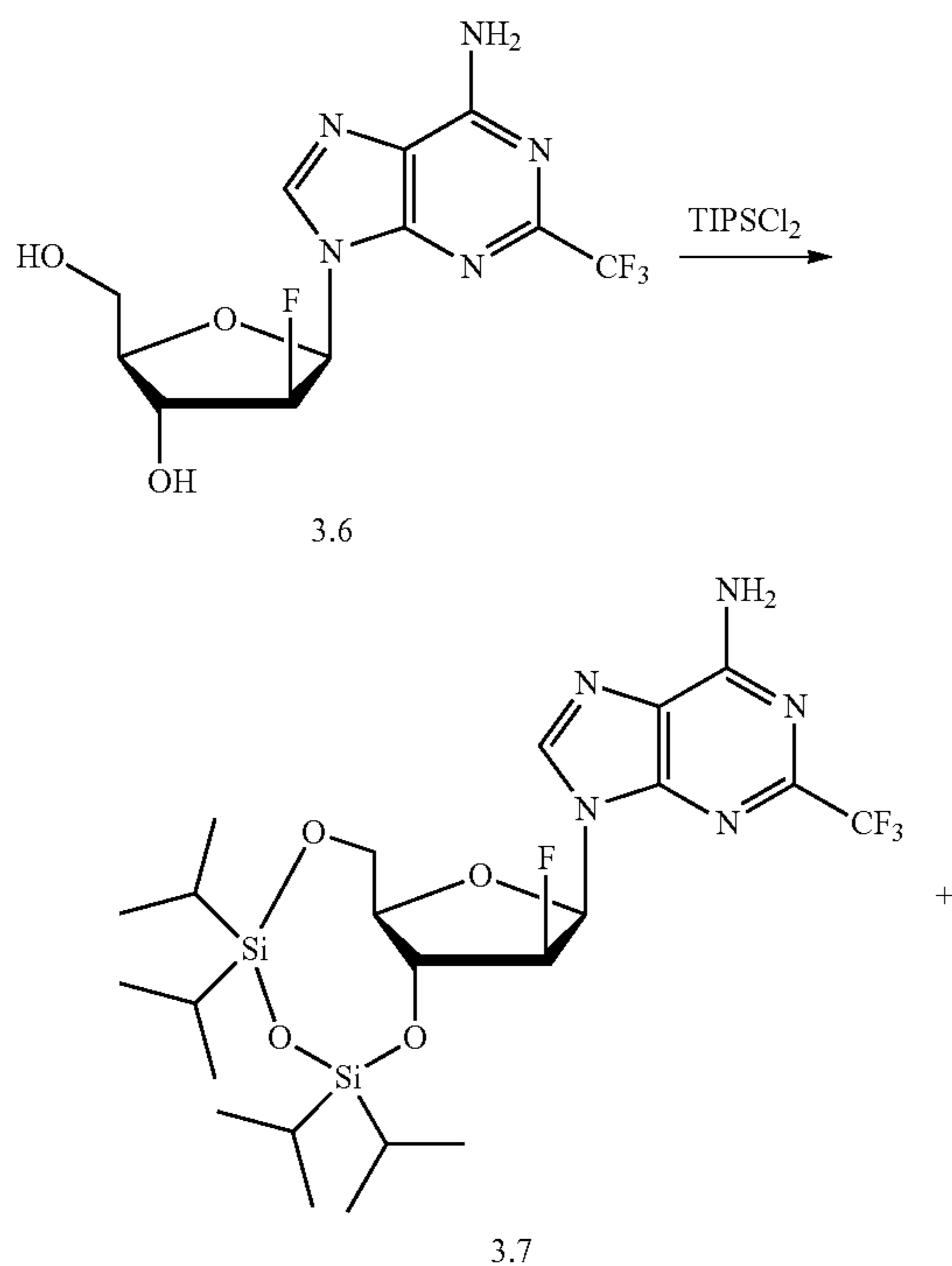
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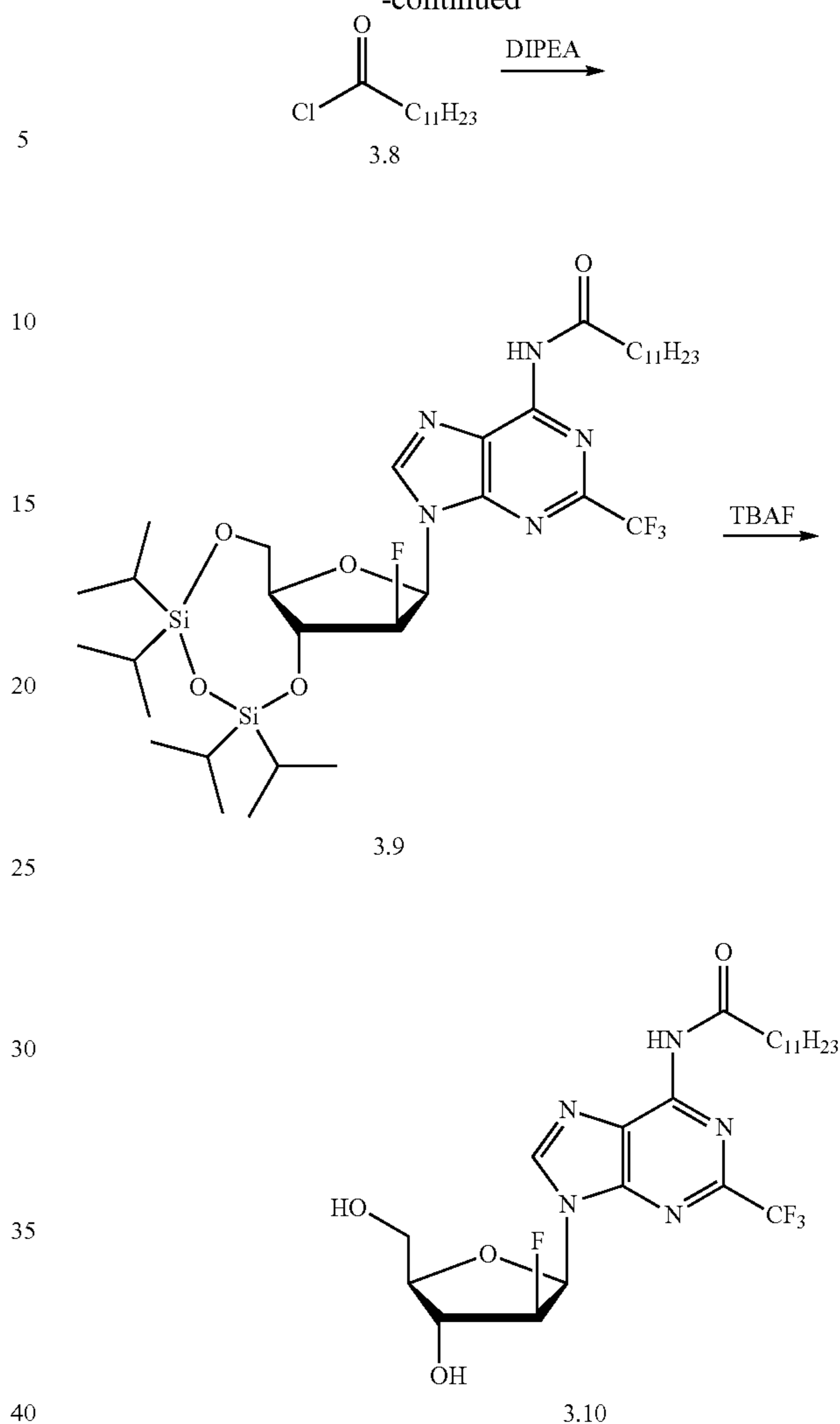
Compounds are represented in generic form, wherein PG¹ is an alcohol protecting group, wherein X is halogen, and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 3B.



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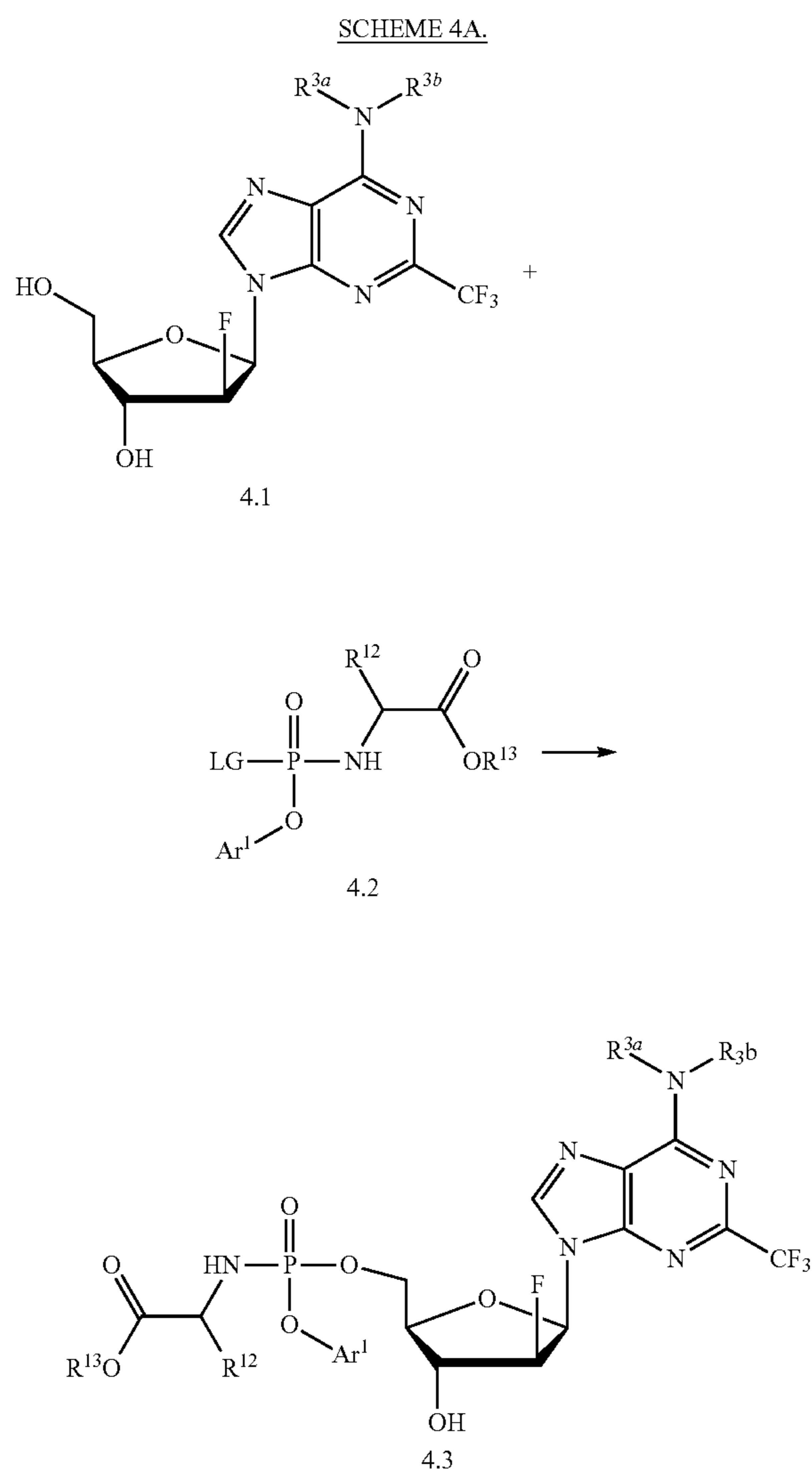


In one aspect, compounds of type 3.10, and similar compounds, can be prepared according to reaction Scheme 3B above. Thus, compounds of type 3.7 can be prepared by protection of an appropriate alcohol, e.g., 3.6 as shown above. The protection reaction is carried out in the presence of an appropriate protecting agent, e.g., 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane as shown above. Compounds of type 3.9 can be prepared by a coupling reaction between an appropriate amine, e.g., 3.7 as shown above, and an appropriate acyl halide, e.g., 3.8 as shown above. Appropriate acyl halides are commercially available or prepared by one of skill in the art. The coupling reaction is carried out in the presence of an appropriate base, e.g., DIPEA as shown above. Compounds of type 3.10 can be prepared by deprotection of an appropriate nucleoside, e.g., 3.9 as shown above. The deprotection reaction is carried out in the presence of an appropriate deprotecting agent, e.g., tetrabutylammonium fluoride (TBAF) as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 3.1, 3.2, and 3.3), can be substituted in the reaction to provide substituted nucleoside derivatives similar to Formula 3.4.

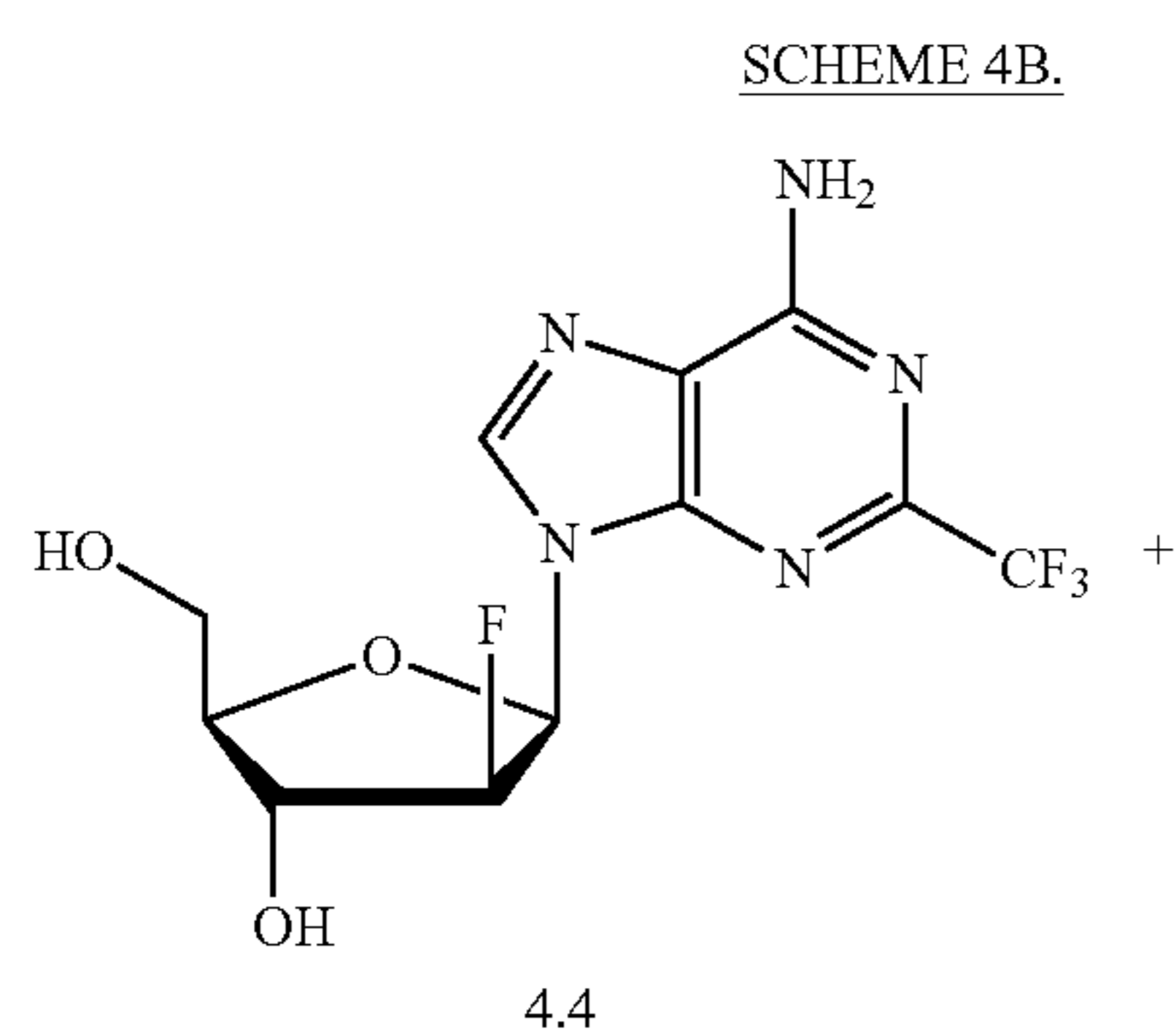
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4. Route IV

In one aspect, a disclosed nucleotide can be prepared as shown below.

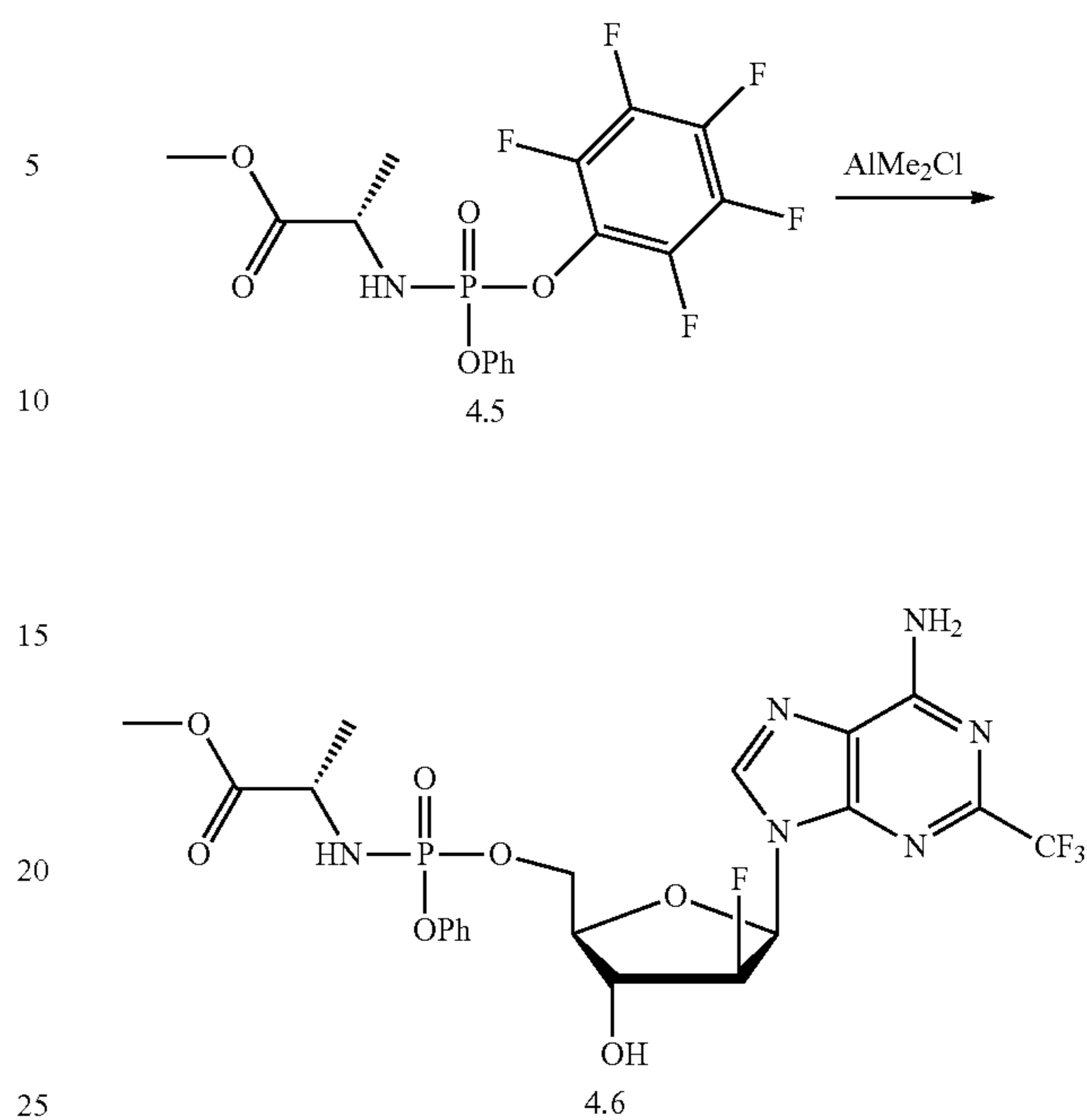


Compounds are represented in generic form, wherein LG is a leaving group, and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.



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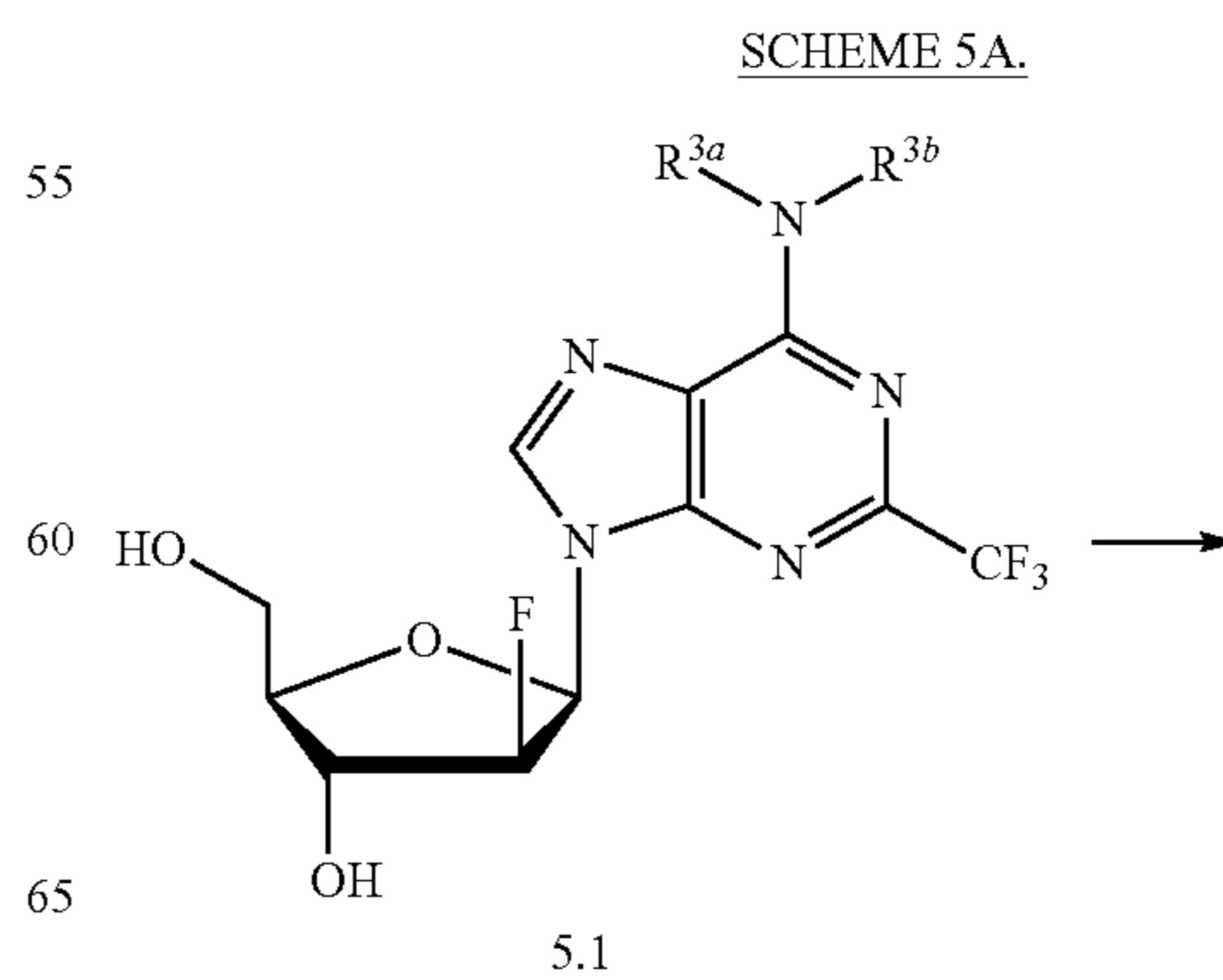
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In one aspect, compounds of type 4.6, and similar compounds, can be prepared according to reaction Scheme 4B above. Thus, compounds of type 4.6 can be prepared by a coupling reaction between an appropriate primary alcohol, e.g., 4.4 as shown above, and an appropriate phosphoramidate, e.g., 4.5 as shown above. Appropriate phosphoramidates are commercially available or prepared by methods known to one of skill in the art. The coupling reaction is carried out in the presence of an appropriate Lewis acid, e.g., trimethylaluminum as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 3.1 and 3.2), can be substituted in the reaction to provide substituted nucleotide derivatives similar to Formula 3.3.

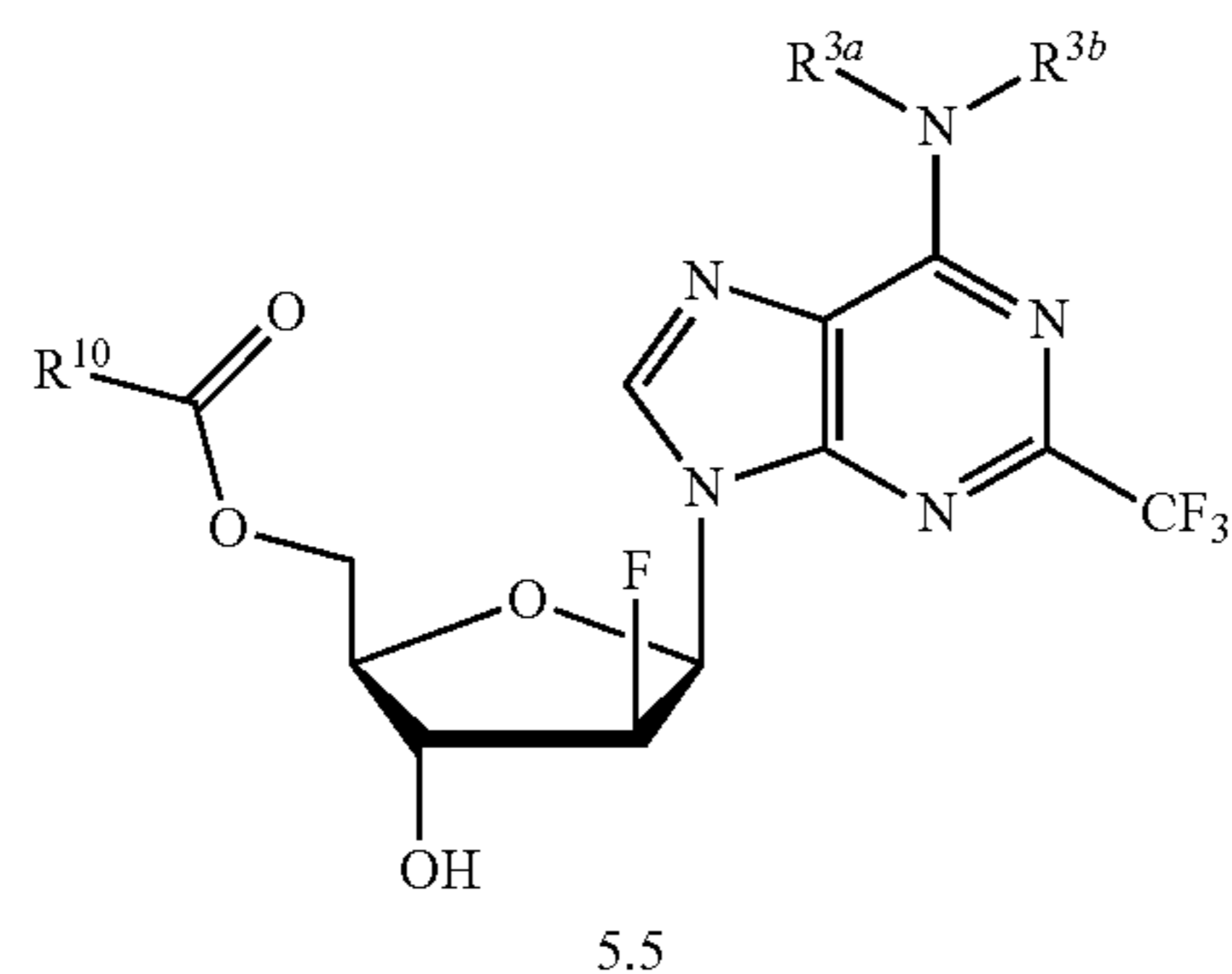
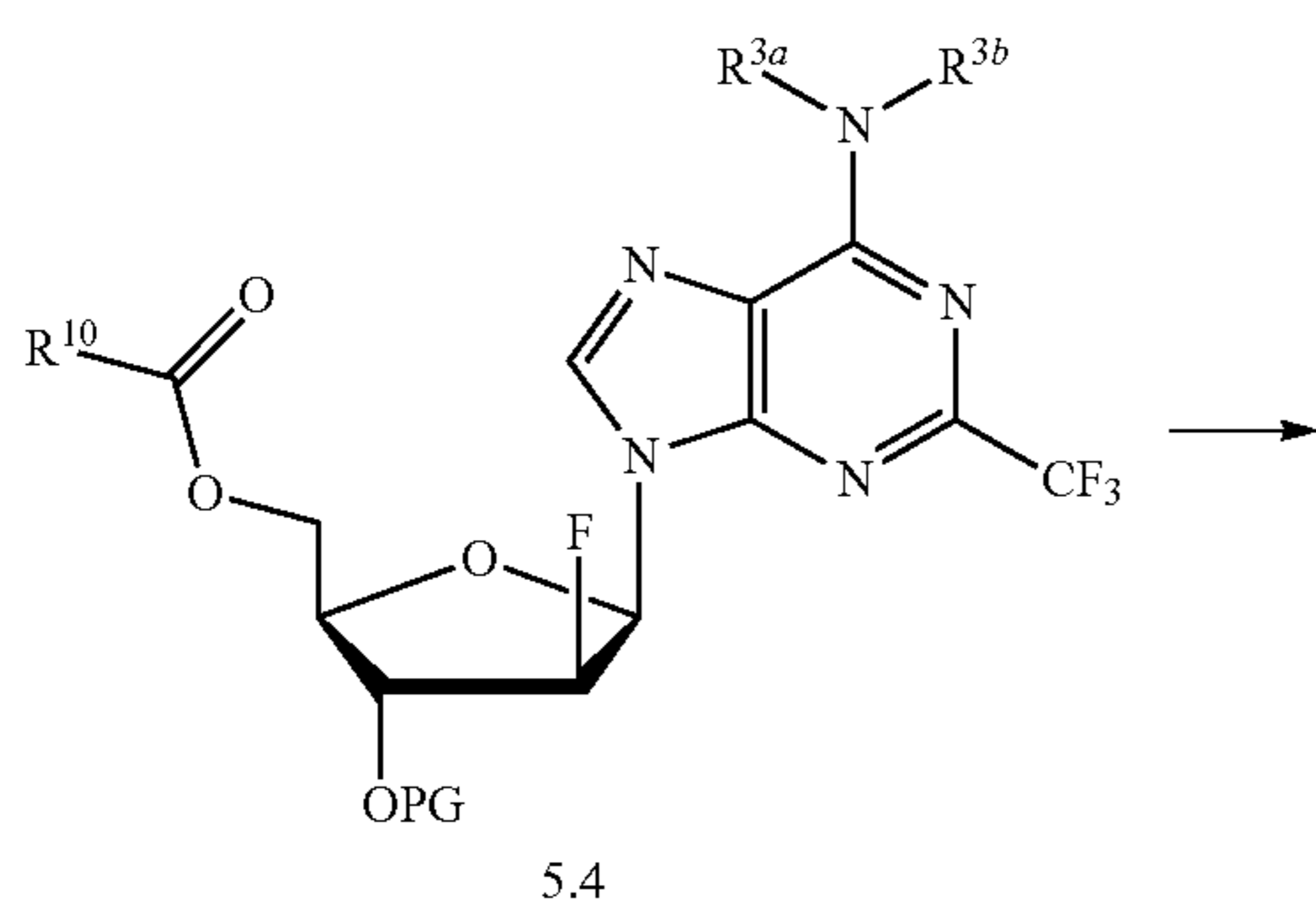
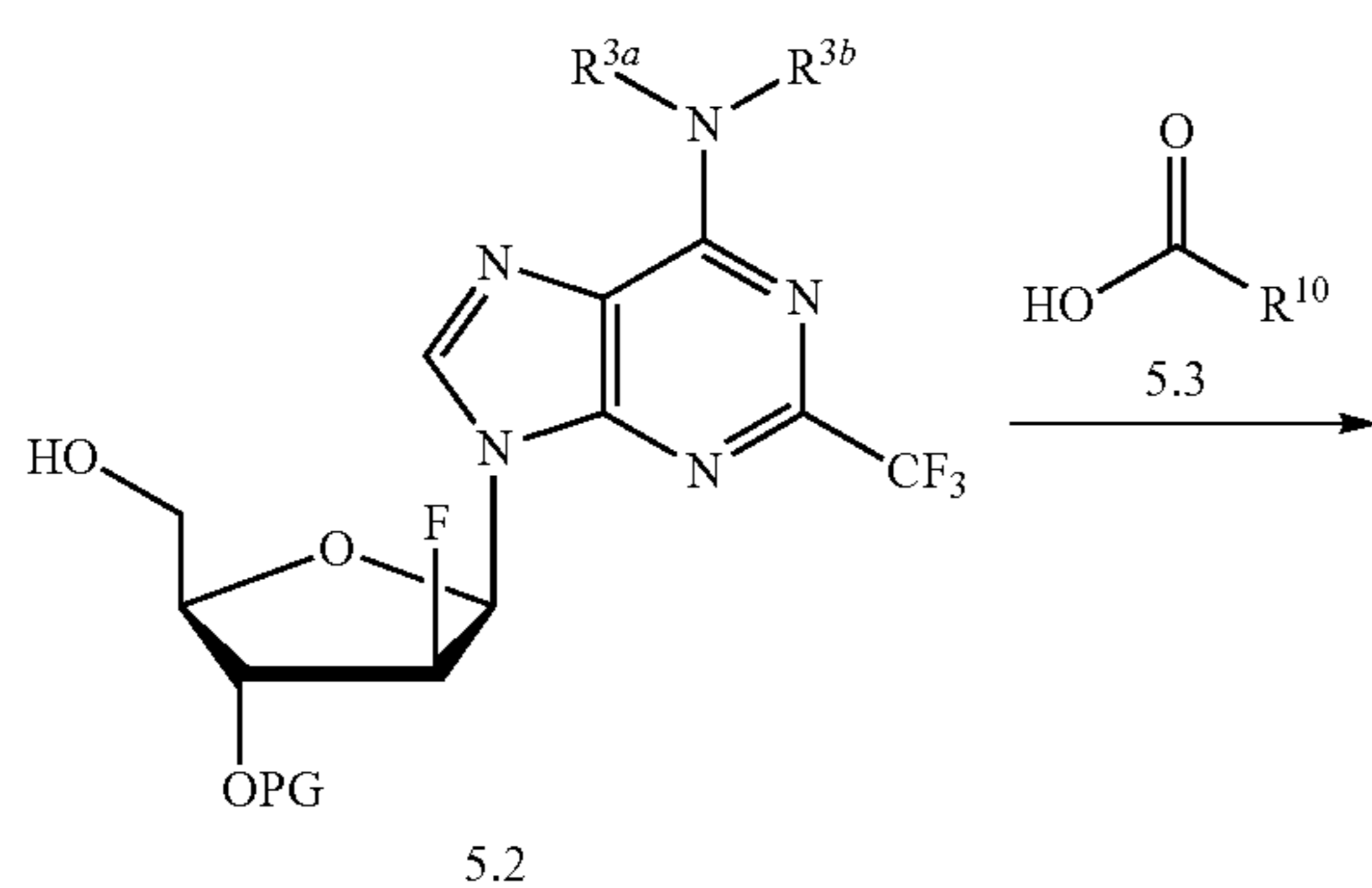
5. Route V

In one aspect, a disclosed nucleoside can be prepared as shown below.



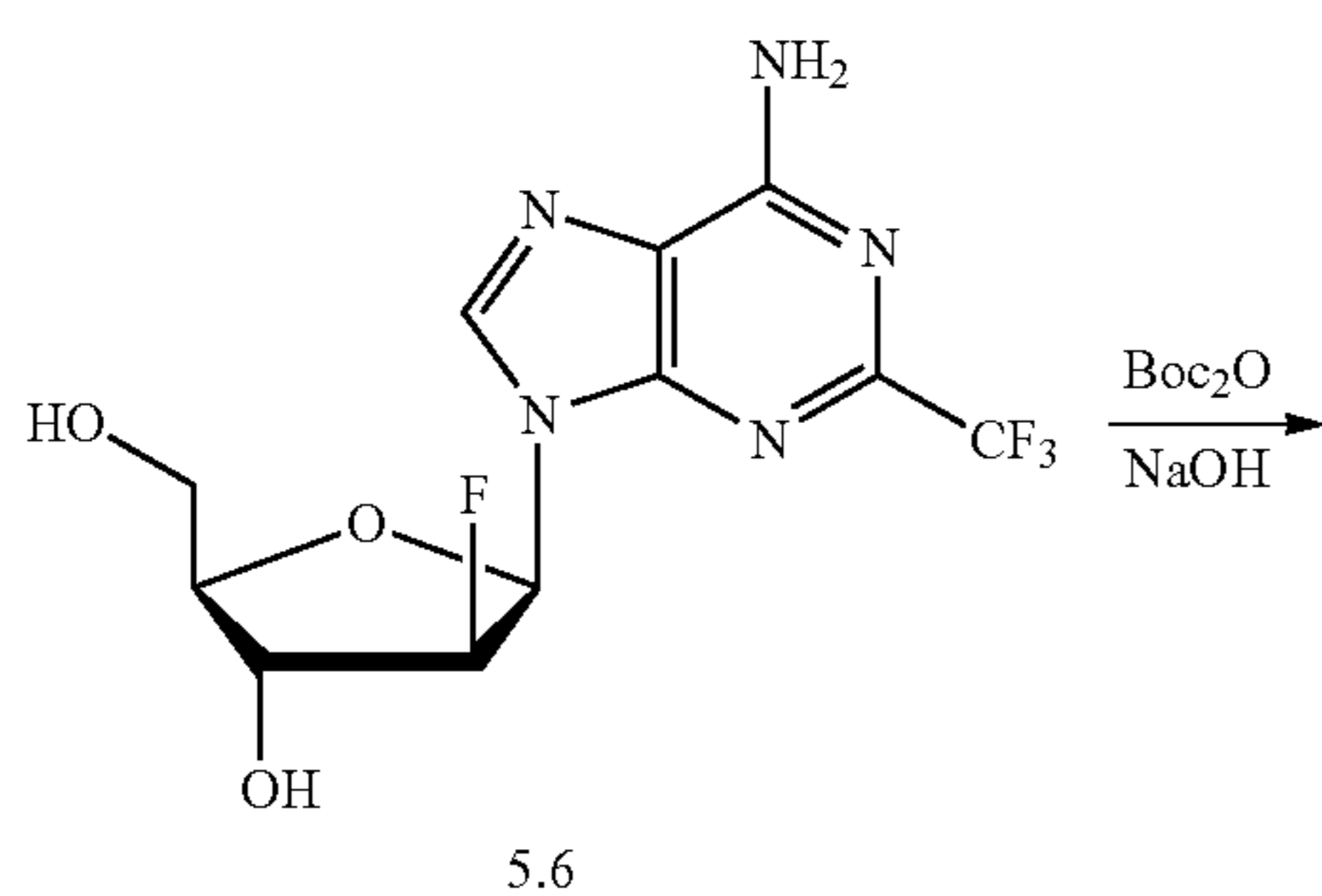
93

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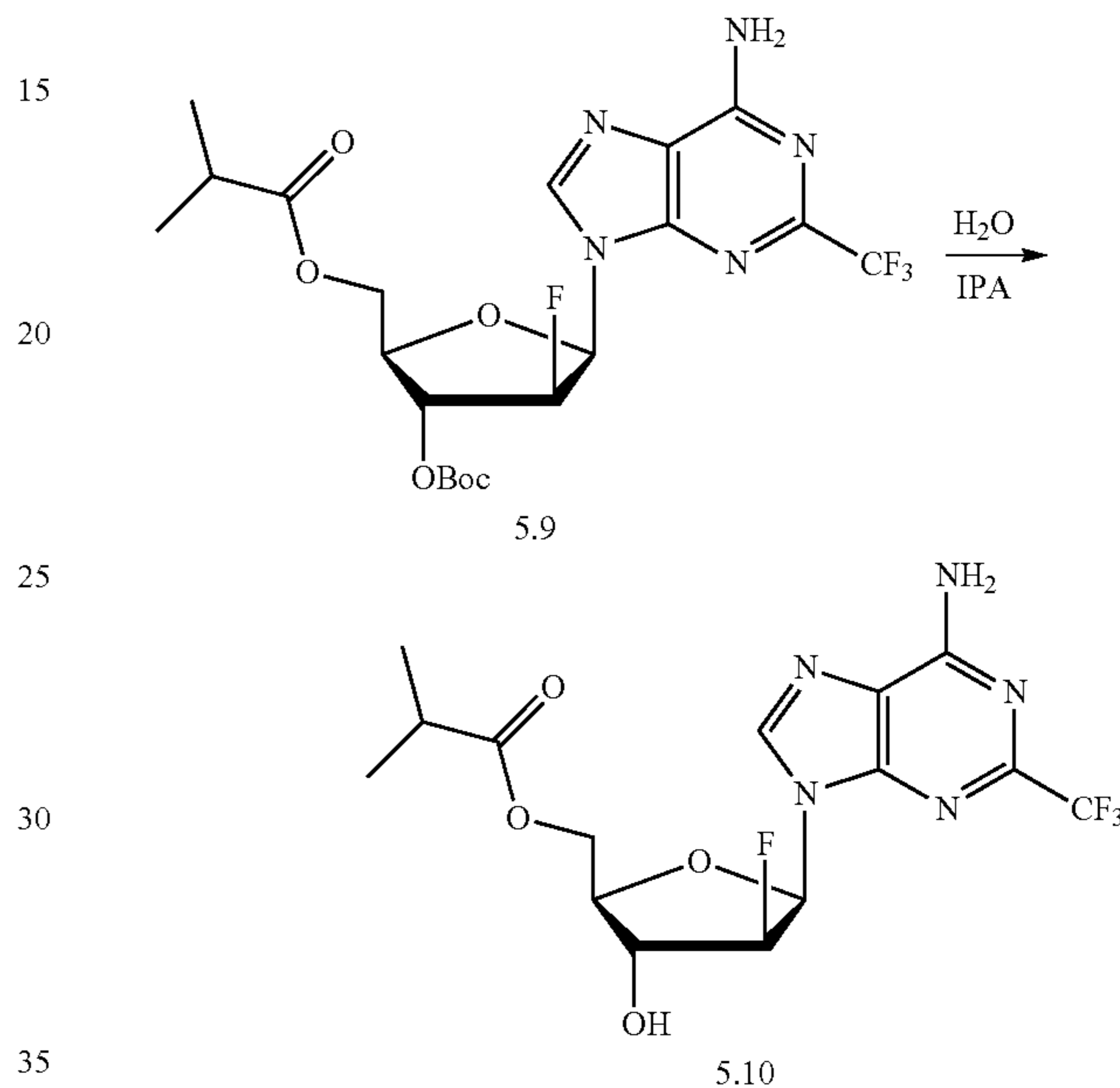
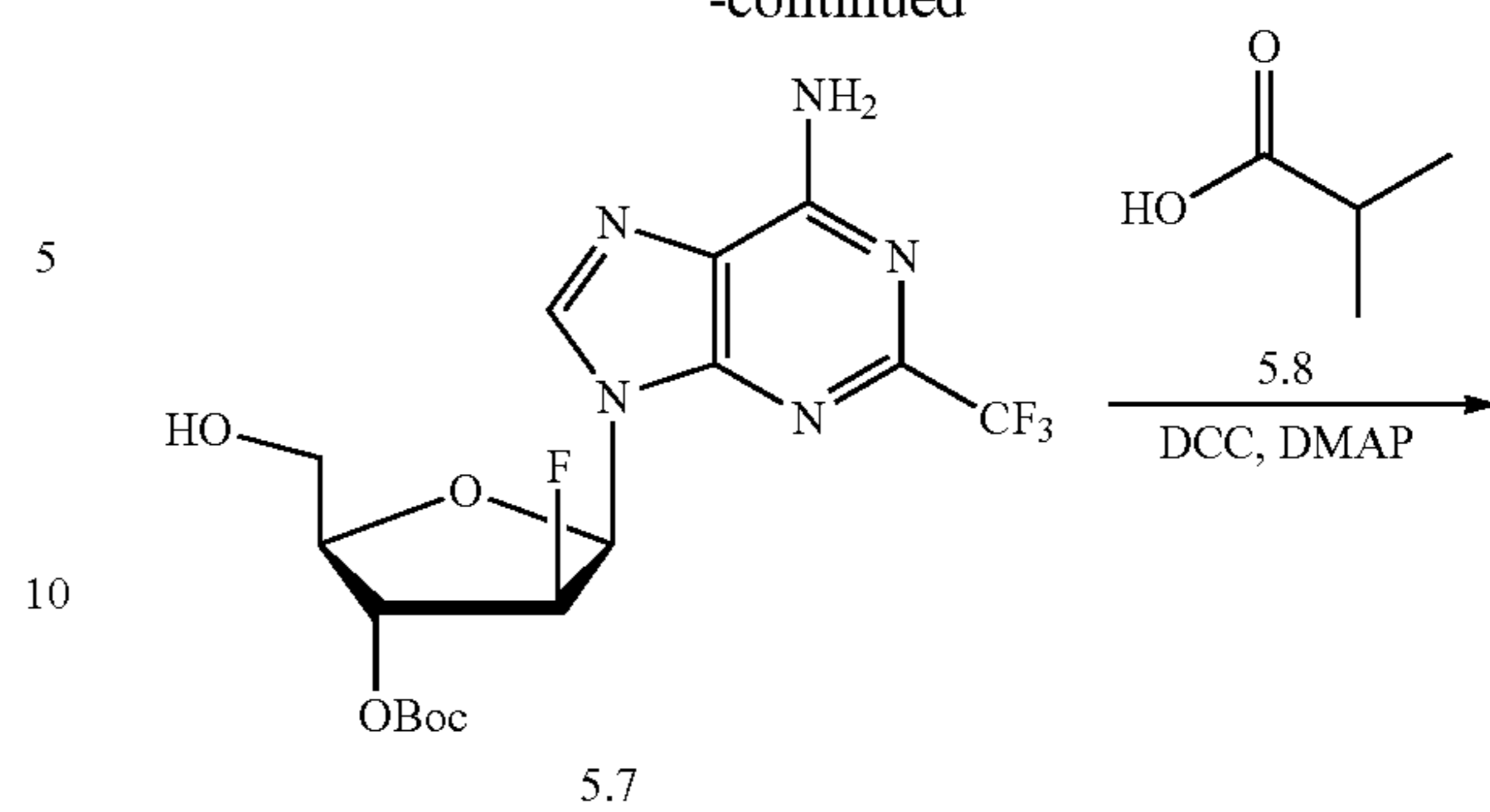
Compounds are represented in generic form, wherein PG is an alcohol protecting group, and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 5B.



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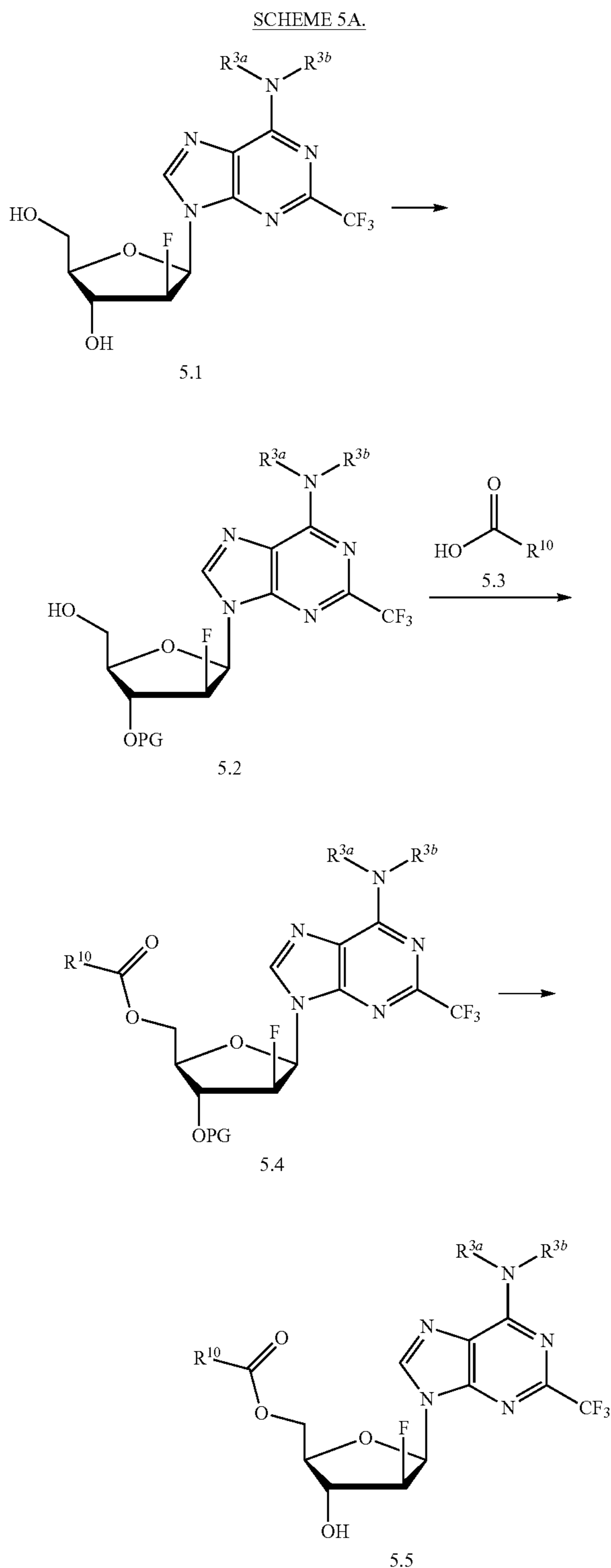


In one aspect, compounds of type 5.10, and similar compounds, can be prepared according to reaction Scheme 5B above. Thus, compounds of type 5.7 can be prepared by protection of an appropriate secondary alcohol, e.g., 5.6 as shown above. The protection is carried out in the presence of an appropriate protecting group, e.g., di-tert-butyl dicarbonates as shown above, and an appropriate base, e.g., sodium hydroxide as shown above. Compounds of type 5.9 can be prepared by a coupling reaction between an appropriate primary alcohol, e.g., 5.7 as shown above, and an appropriate carboxylic acid, e.g., 5.8 as shown above. Appropriate carboxylic acids are commercially available or prepared by methods known to one of skill in the art. The coupling reaction is carried out in the presence of an appropriate coupling agent, e.g., N,N'-dicyclohexylcarbodiimide (DCC) as shown above, an appropriate activating agent, e.g., 4-dimethylaminopyridine (DMAP) as shown above. Compounds of type 5.10 can be prepared by deprotection of an appropriate nucleoside, e.g., 5.9 as shown above. The deprotection is carried out in the presence of an appropriate base, e.g., isopropyl alcohol (IPA) as shown above, in an appropriate solvent, e.g., water as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 5.1, 5.2, 5.3, and 5.4), can be substituted in the reaction to provide substituted nucleoside derivatives similar to Formula 5.5.

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6. Route V

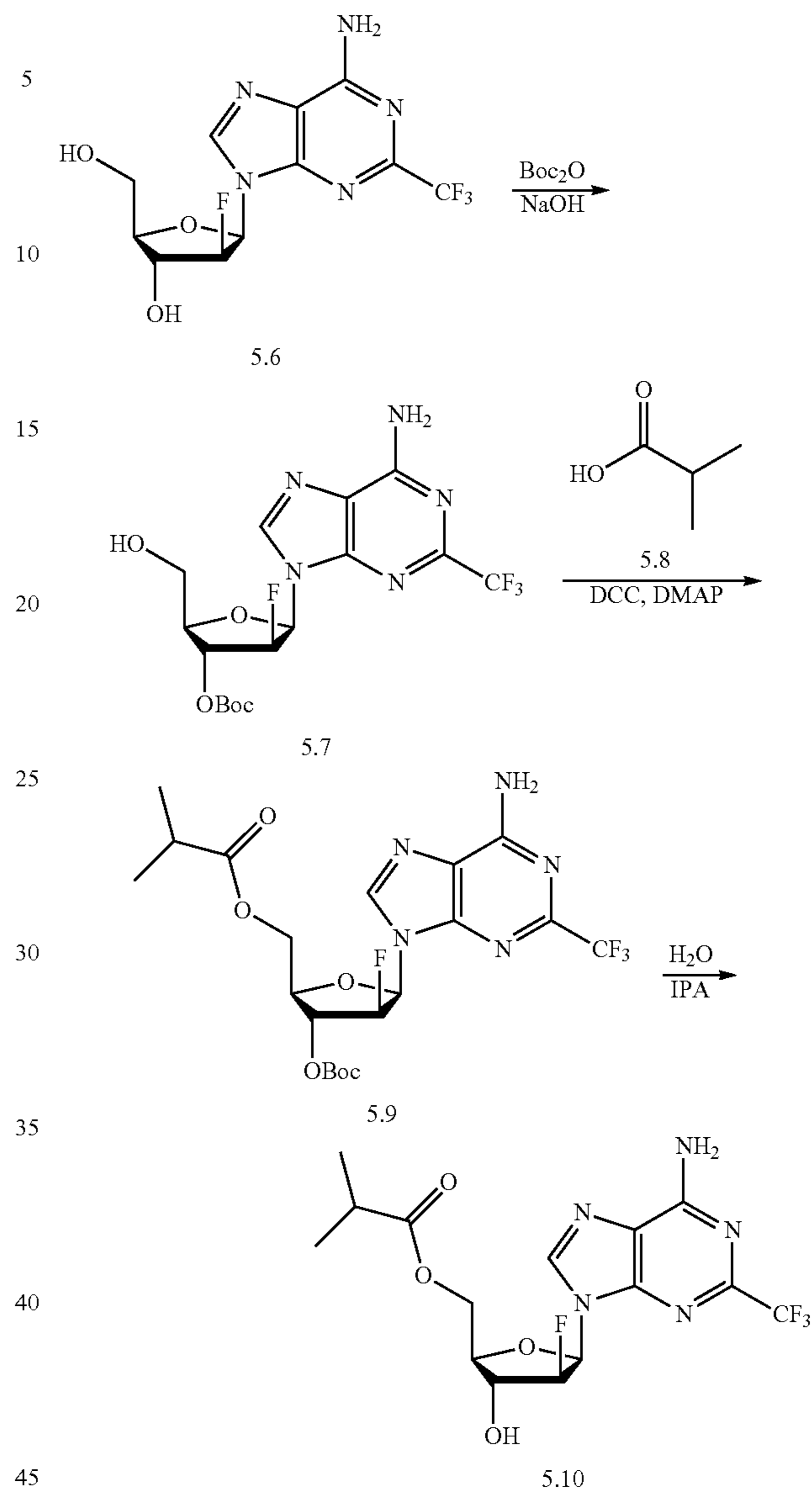
In one aspect, a disclosed nucleoside can be prepared as shown below.



Compounds are represented in generic form, wherein PG is an alcohol protecting group, and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

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SCHEME 5B.



In one aspect, compounds of type 5.10, and similar compounds, can be prepared according to reaction Scheme 5B above. Thus, compounds of type 5.7 can be prepared by protection of an appropriate secondary alcohol, e.g., 5.6 as shown above. The protection is carried out in the presence of an appropriate protecting group, e.g., di-tert-butyl dicarbonates as shown above, and an appropriate base, e.g., sodium hydroxide as shown above. Compounds of type 5.9 can be prepared by a coupling reaction between an appropriate primary alcohol, e.g., 5.7 as shown above, and an appropriate carboxylic acid, e.g., 5.8 as shown above. Appropriate carboxylic acids are commercially available or prepared by methods known to one of skill in the art. The coupling reaction is carried out in the presence of an appropriate coupling agent, e.g., N,N'-dicyclohexylcarbodiimide (DCC) as shown above, an appropriate activating agent, e.g., 4-dimethylaminopyridine (DMAP) as shown above. Compounds of type 5.10 can be prepared by deprotection of an appropriate nucleoside, e.g., 5.9 as shown above. The deprotection is carried out in the presence of an

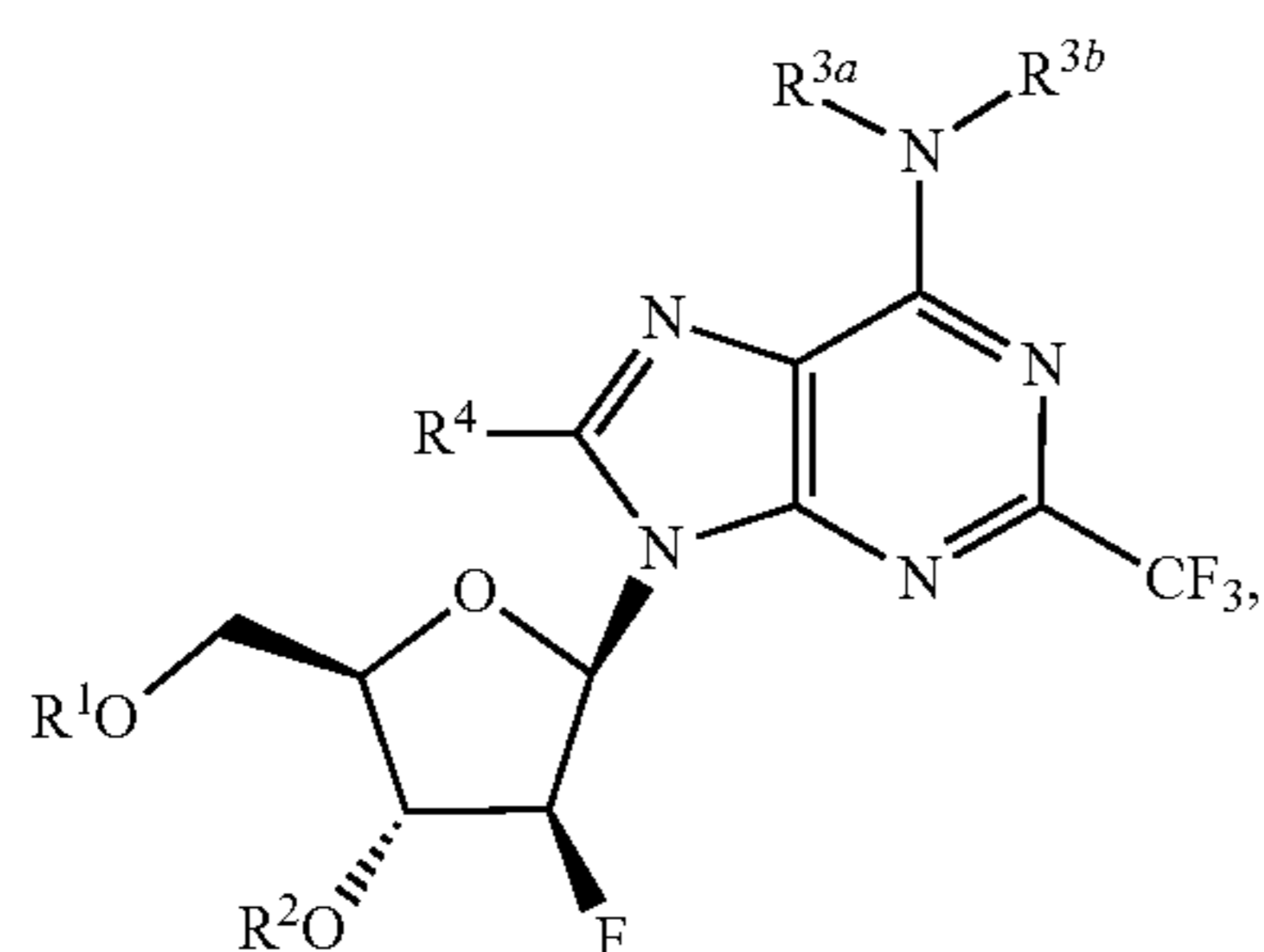
97

appropriate base, e.g., isopropyl alcohol (IPA) as shown above, in an appropriate solvent, e.g., water as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 5.1, 5.2, 5.3, and 5.4), can be substituted in the reaction to provide substituted nucleoside derivatives similar to Formula 5.5.

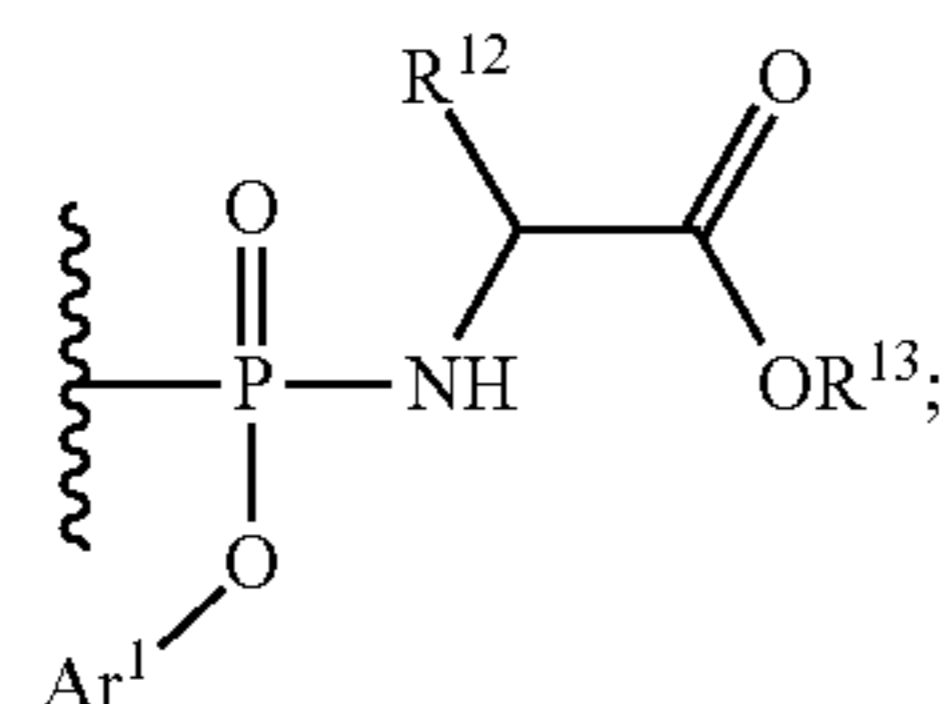
D. Pharmaceutical Compositions

In one aspect, disclosed are pharmaceutical compositions comprising a disclosed compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Thus, in one aspect, disclosed are pharmaceutical compositions comprising a compound having a structure represented by a formula:



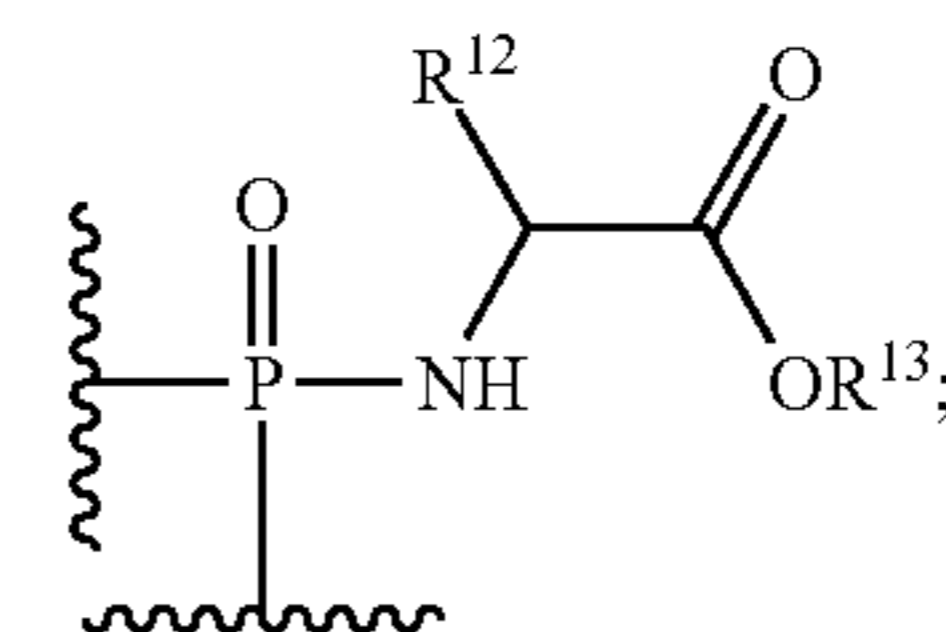
wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:



wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(C1-C8 \text{ alkyl})NHC(NH)NH_2$, $-(C1-C8 \text{ alkyl})CO_2H$, $-(C1-C8 \text{ alkyl})C(O)NH_2$, Cy^1 , and $-(C1-C8 \text{ alkyl})Cy^1$; wherein Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $-(C1-C10 \text{ alkyl})CO_2(C1-C10 \text{ alkyl})$, $-(C1-C10 \text{ alkyl})CO_2(C1-C10 \text{ alkylthiol})$, $-(C1-C10 \text{ alkyl})-S-S-(C1-C10 \text{ alkyl})$, and Ar^2 ; wherein Ar^2 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$,

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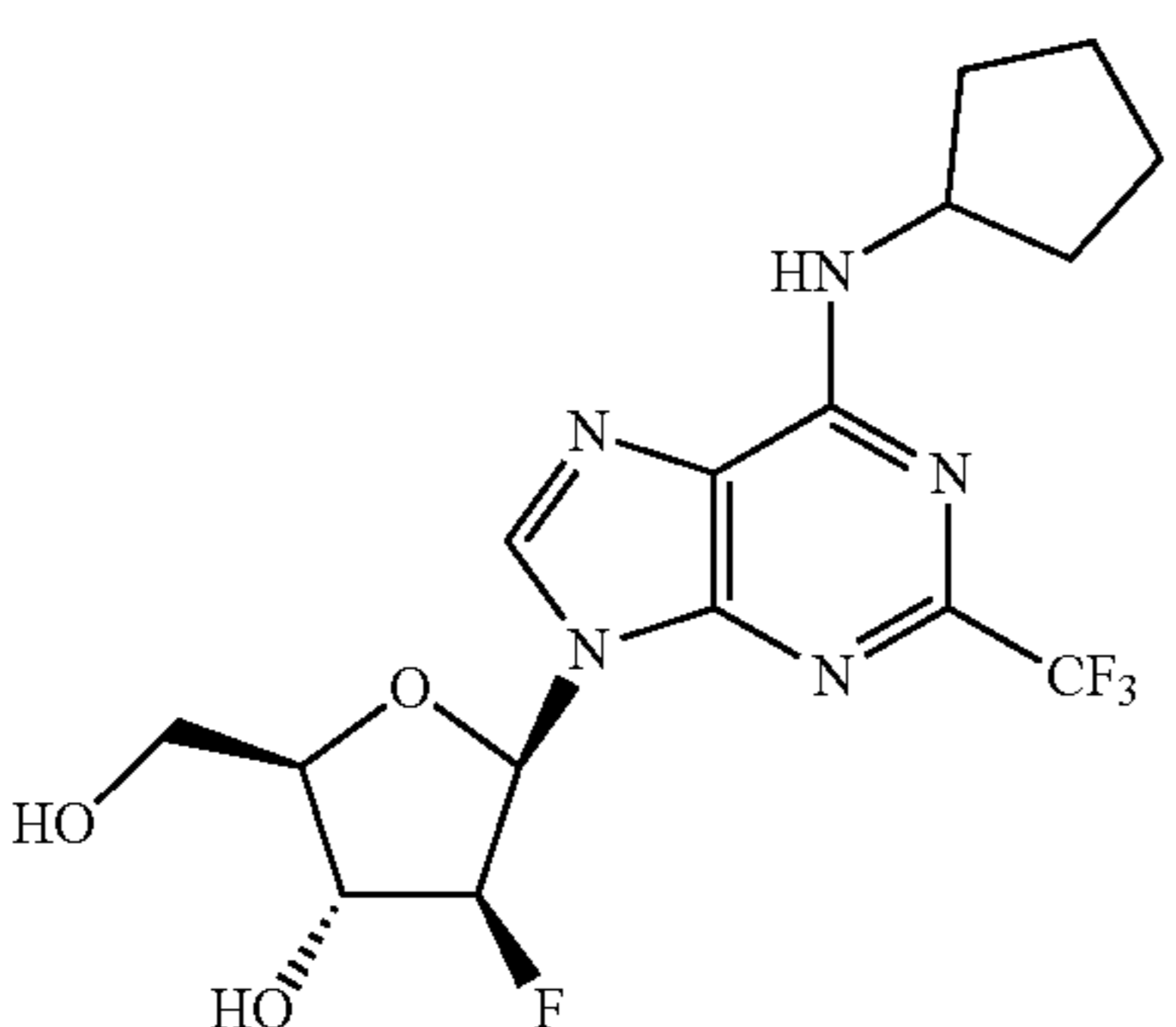
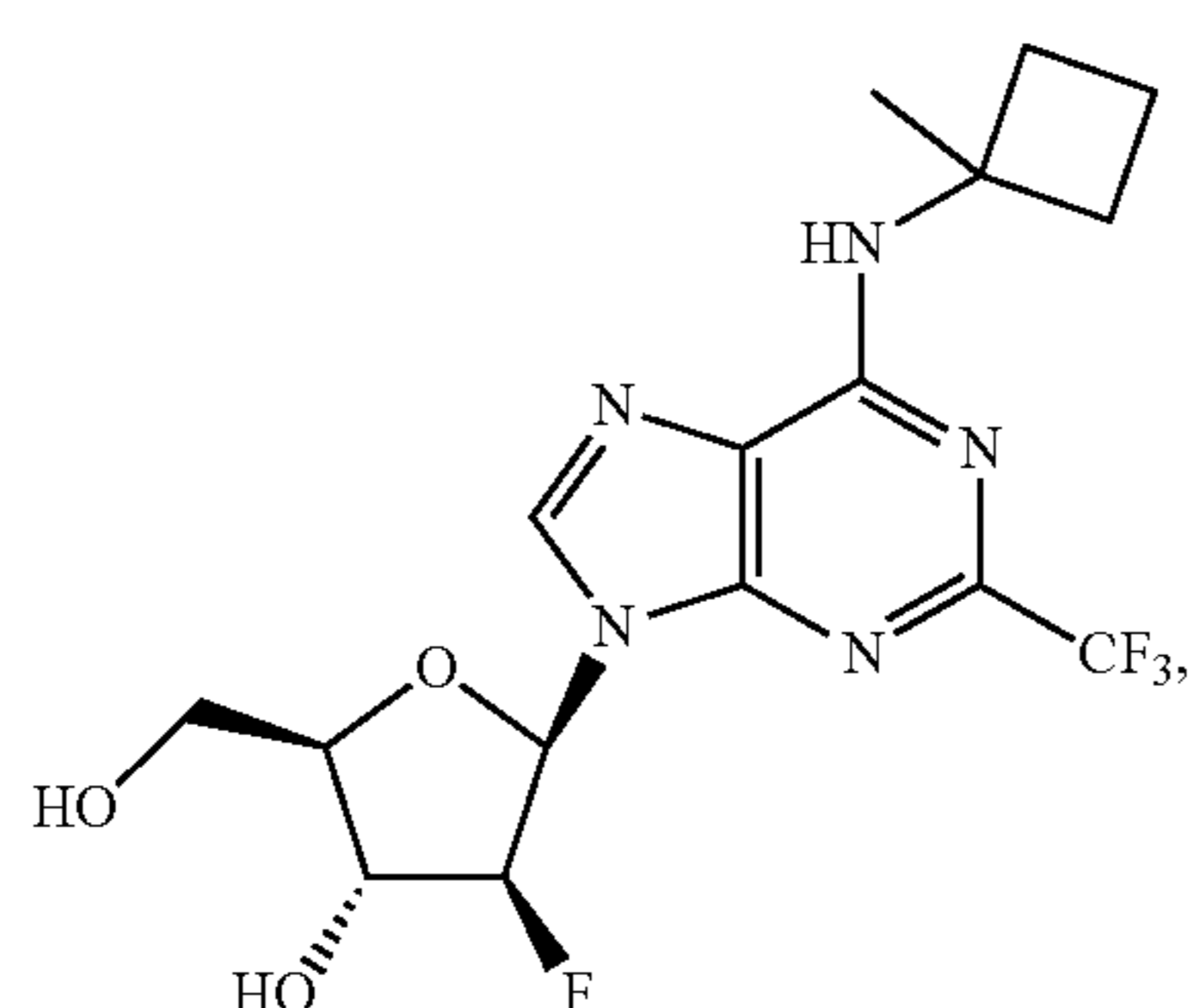
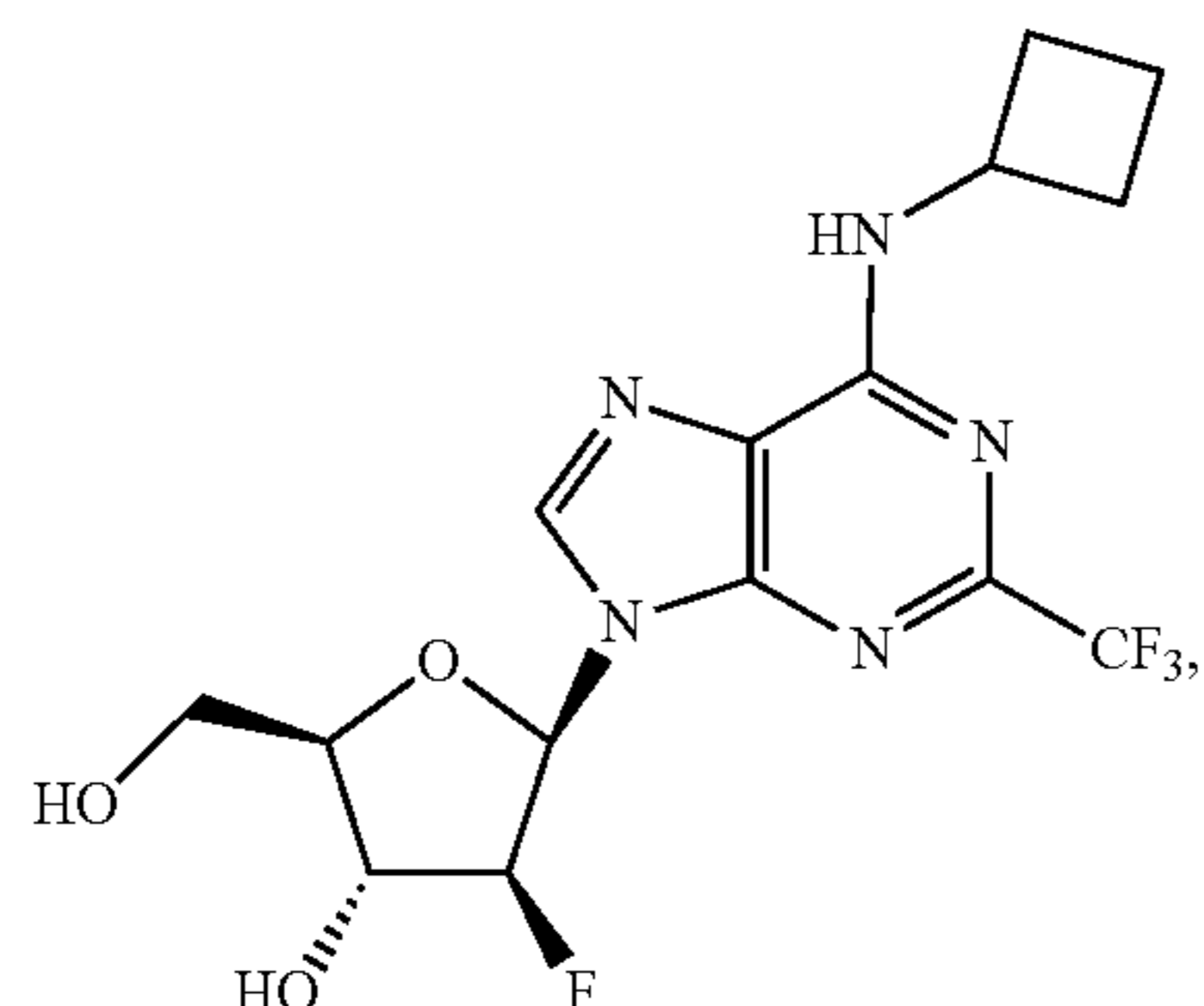
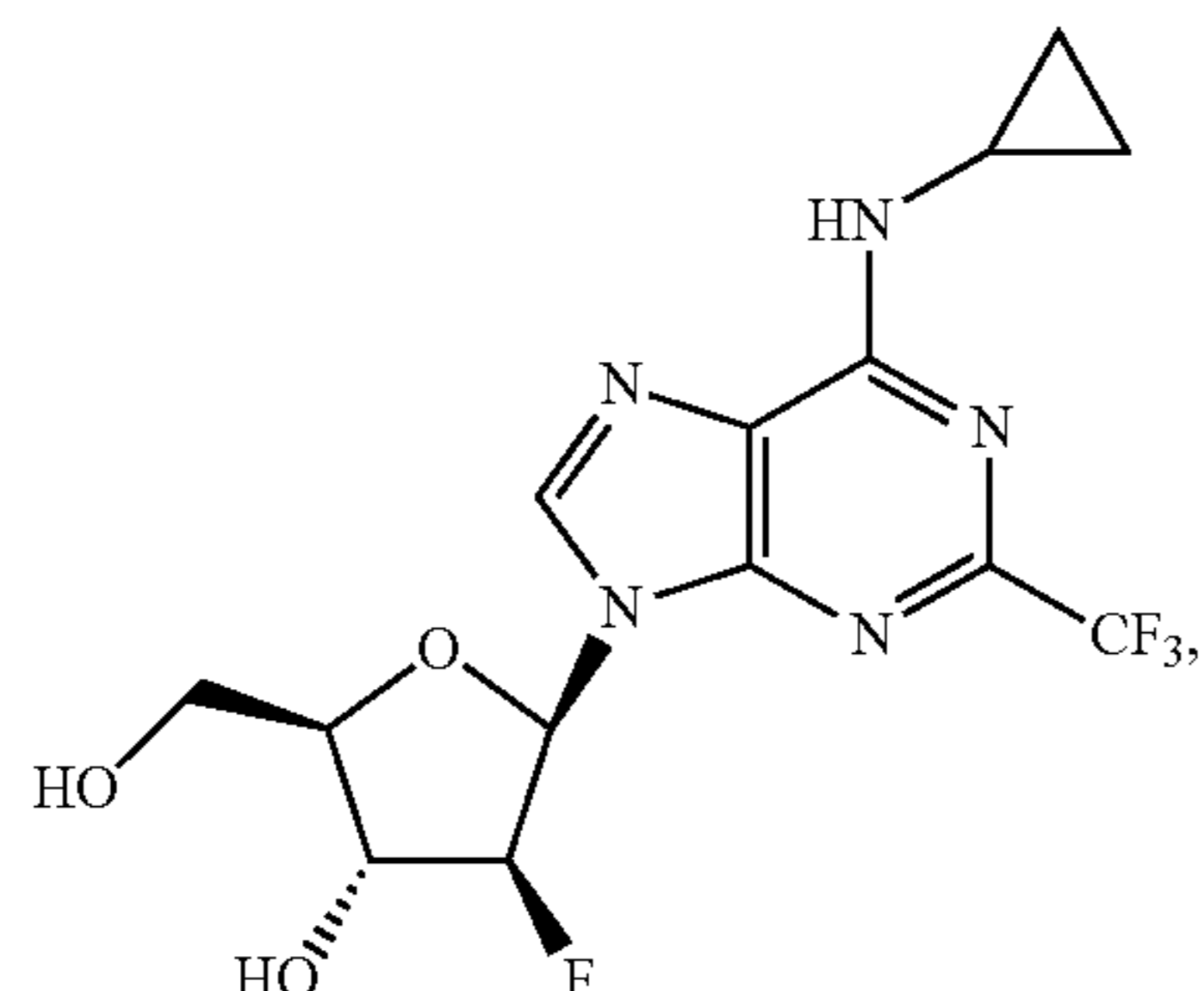
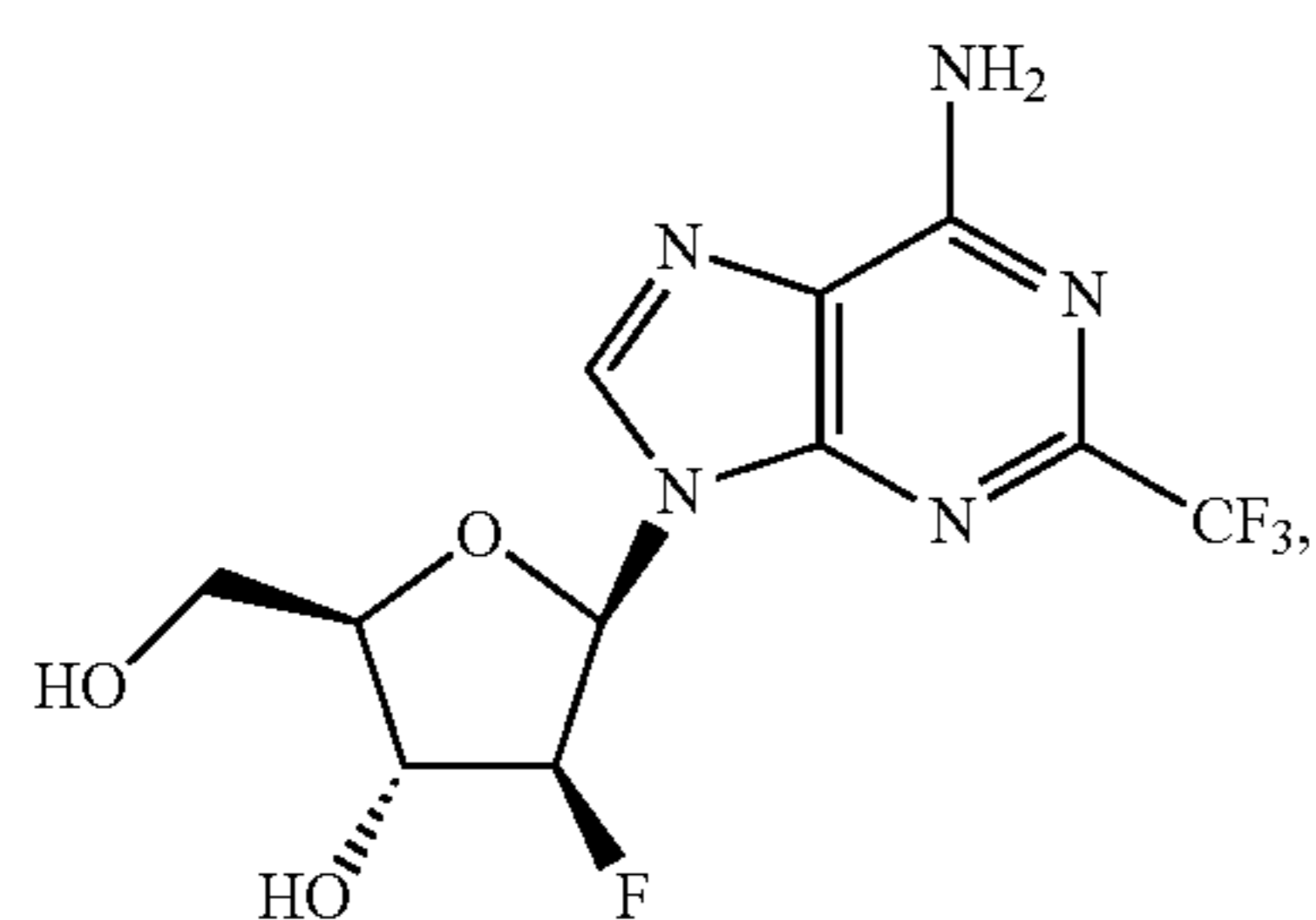
$-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-OH$, C1-C12 alkyl, C1-C12 alkoxy, $-C(O)R^{14}$, $-(C1-C12 \text{ alkyl})CO_2H$, and $-(C1-C6 \text{ alkyl})Cy^2$, provided that R^{3a} and R^{3b} are not simultaneously hydrogen; wherein R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{21}$; wherein R^{21} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(C1-C8 \text{ alkyl})NHC(NH)NH_2$, $-(C1-C8 \text{ alkyl})CO_2H$, $-(C1-C8 \text{ alkyl})C(O)NH_2$, Cy^3 , and $-(C1-C8 \text{ alkyl})Cy^3$; wherein Cy^3 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy^2 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine, provided that when each of R^1 and R^2 is hydrogen, then at least one of R^{3a} and R^{3b} is a non-hydrogen group, and provided that when one of R^{3a} and R^{3b} is $-(C1-C6 \text{ alkyl})Cy^2$, then R^1 is hydrogen, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

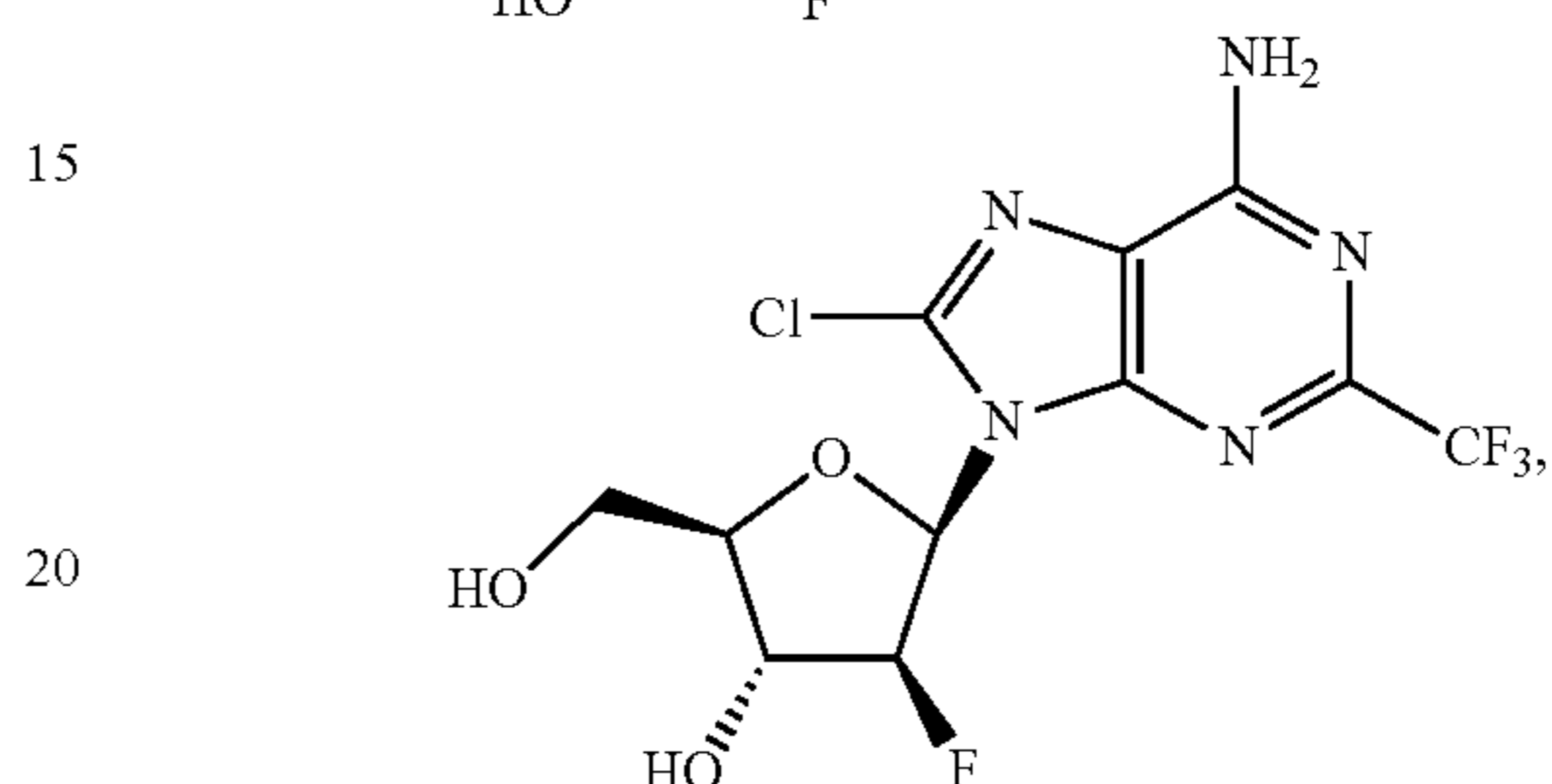
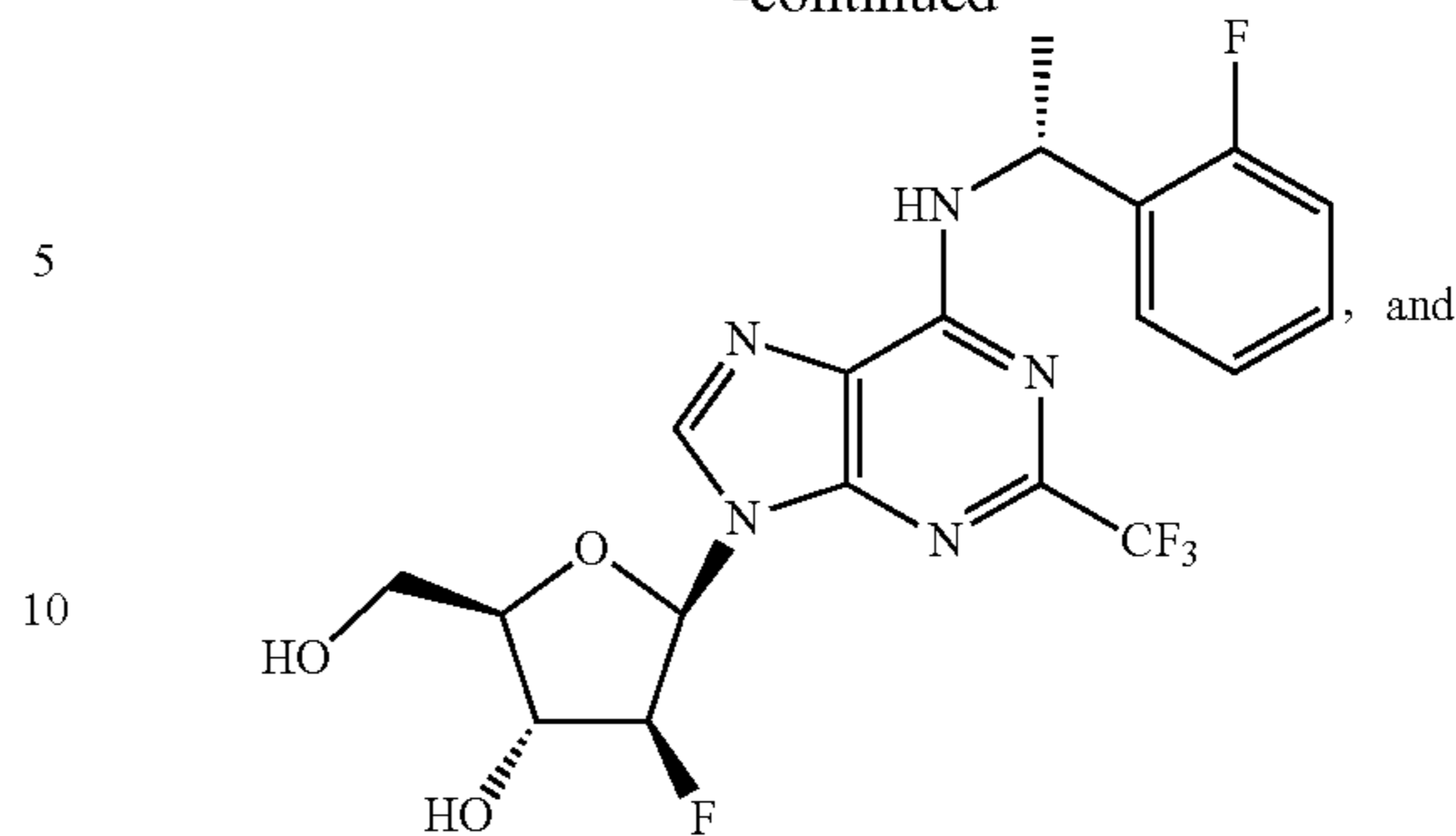
In one aspect, disclosed are pharmaceutical compositions comprising a compound having a structure selected from:

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25 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In various aspects, the compounds and compositions of the invention can be administered in pharmaceutical compositions, which are formulated according to the intended method of administration. The compounds and compositions described herein can be formulated in a conventional manner using one or more physiologically acceptable carriers or excipients. For example, a pharmaceutical composition can be formulated for local or systemic administration, intravenous, topical, or oral administration.

The nature of the pharmaceutical compositions for administration is dependent on the mode of administration and can readily be determined by one of ordinary skill in the art. In various aspects, the pharmaceutical composition is sterile or sterilizable. The therapeutic compositions featured in the invention can contain carriers or excipients, many of which are known to skilled artisans. Excipients that can be used include buffers (for example, citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, polypeptides (for example, serum albumin), EDTA, sodium chloride, liposomes, mannitol, sorbitol, water, and glycerol. The nucleic acids, polypeptides, small molecules, and other modulatory compounds featured in the invention can be administered by any standard route of administration. For example, administration can be parenteral, intravenous, subcutaneous, or oral. A modulatory compound can be formulated in various ways, according to the corresponding route of administration. For example, liquid solutions can be made for administration by drops into the ear, for injection, or for ingestion; gels or powders can be made for ingestion or topical application. Methods for making such formulations are well known and can be found in, for example, Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, PA 1990.

In various aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and

intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In various aspects, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets can be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof

in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt % to about 10 wt % of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

In a further aspect, an effective amount is a therapeutically effective amount. In a still further aspect, an effective amount is a prophylactically effective amount.

In a further aspect, the pharmaceutical composition is administered to a mammal. In a still further aspect, the mammal is a human. In an even further aspect, the human is a patient.

In a further aspect, the pharmaceutical composition is used to treat a disorder of uncontrolled cellular proliferation such as, for example, cancers including, but not limited to, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

It is understood that the disclosed compositions can be prepared from the disclosed compounds. It is also under-

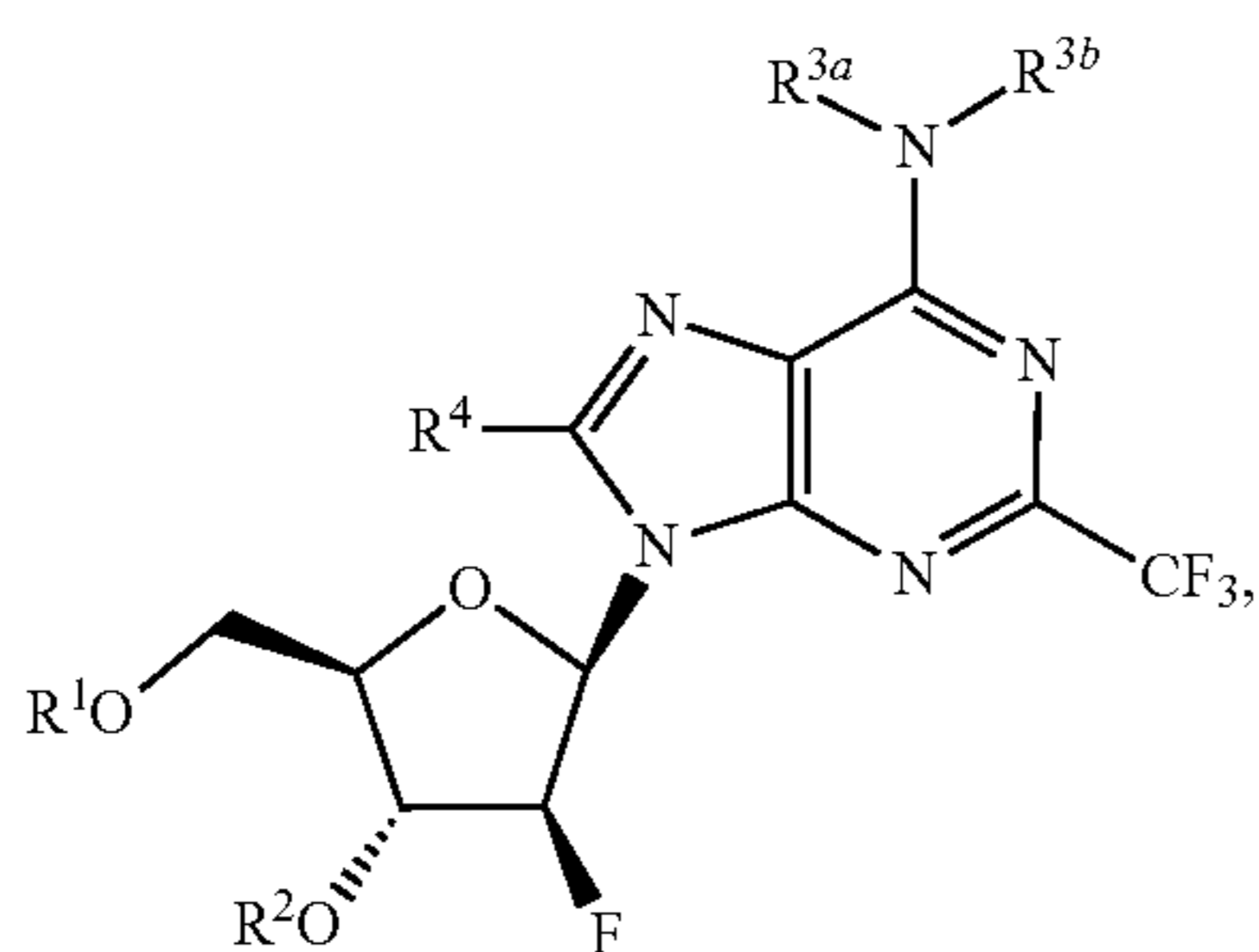
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stood that the disclosed compositions can be employed in the disclosed methods of using.

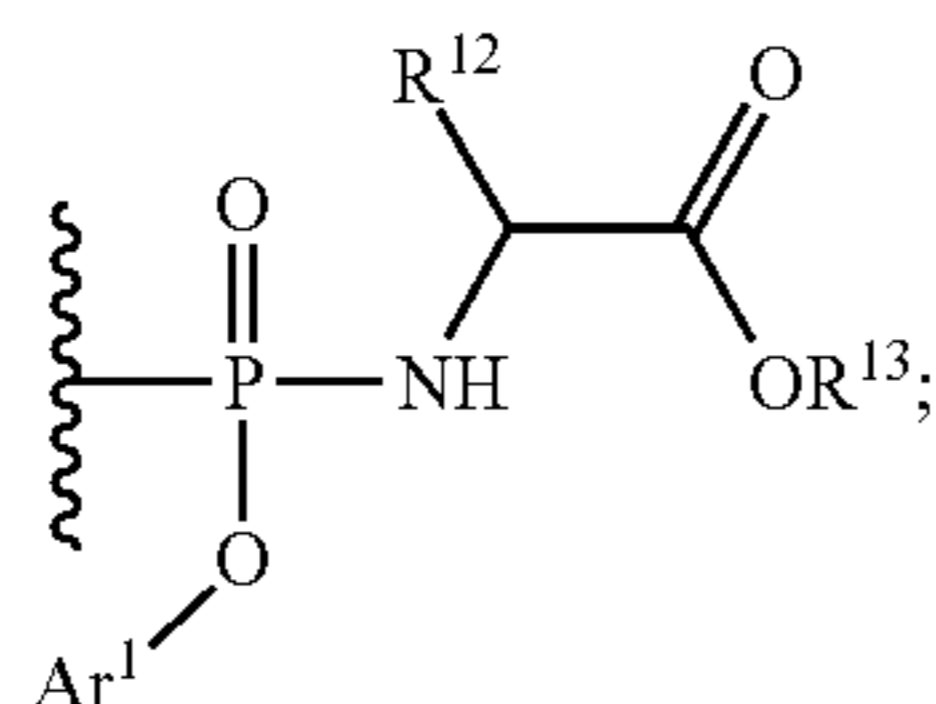
E. Methods of Treating Cancer in a Subject

In one aspect, disclosed are methods of treating cancer in a subject, the method comprising the step of administering to the subject an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

Thus, in one aspect, disclosed are methods of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound having a structure represented by a formula:



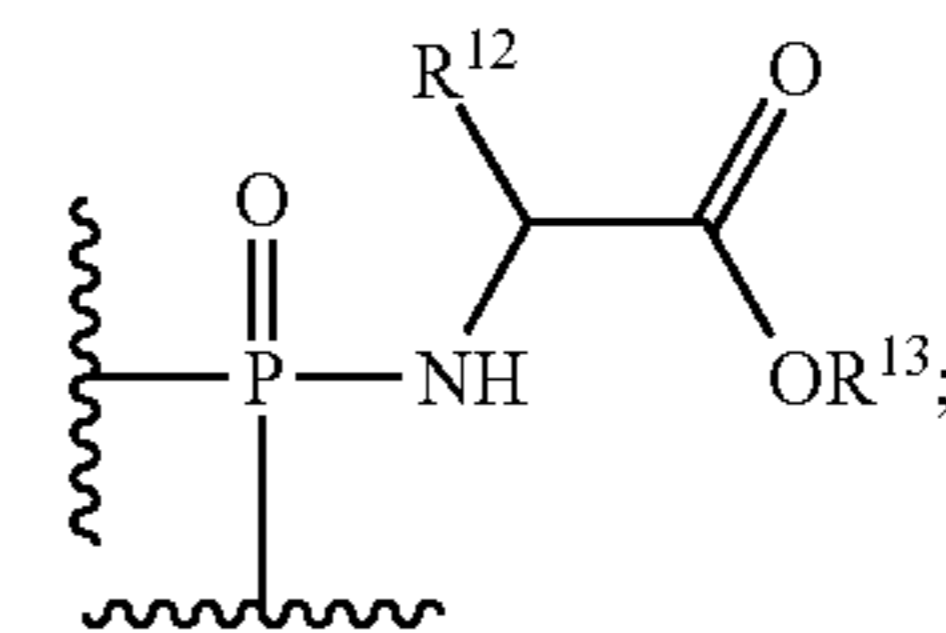
wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:



wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)\text{R}^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8 alkyl})\text{CO}_2\text{H}$, $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^1 , and $-(\text{C1-C8 alkyl})\text{Cy}^1$; wherein Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkyl})$, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkylthiol})$, $-(\text{C1-C10 alkyl})\text{S}-\text{S}-(\text{C1-C10 alkyl})$, and Ar^2 ; wherein Ar^2 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10

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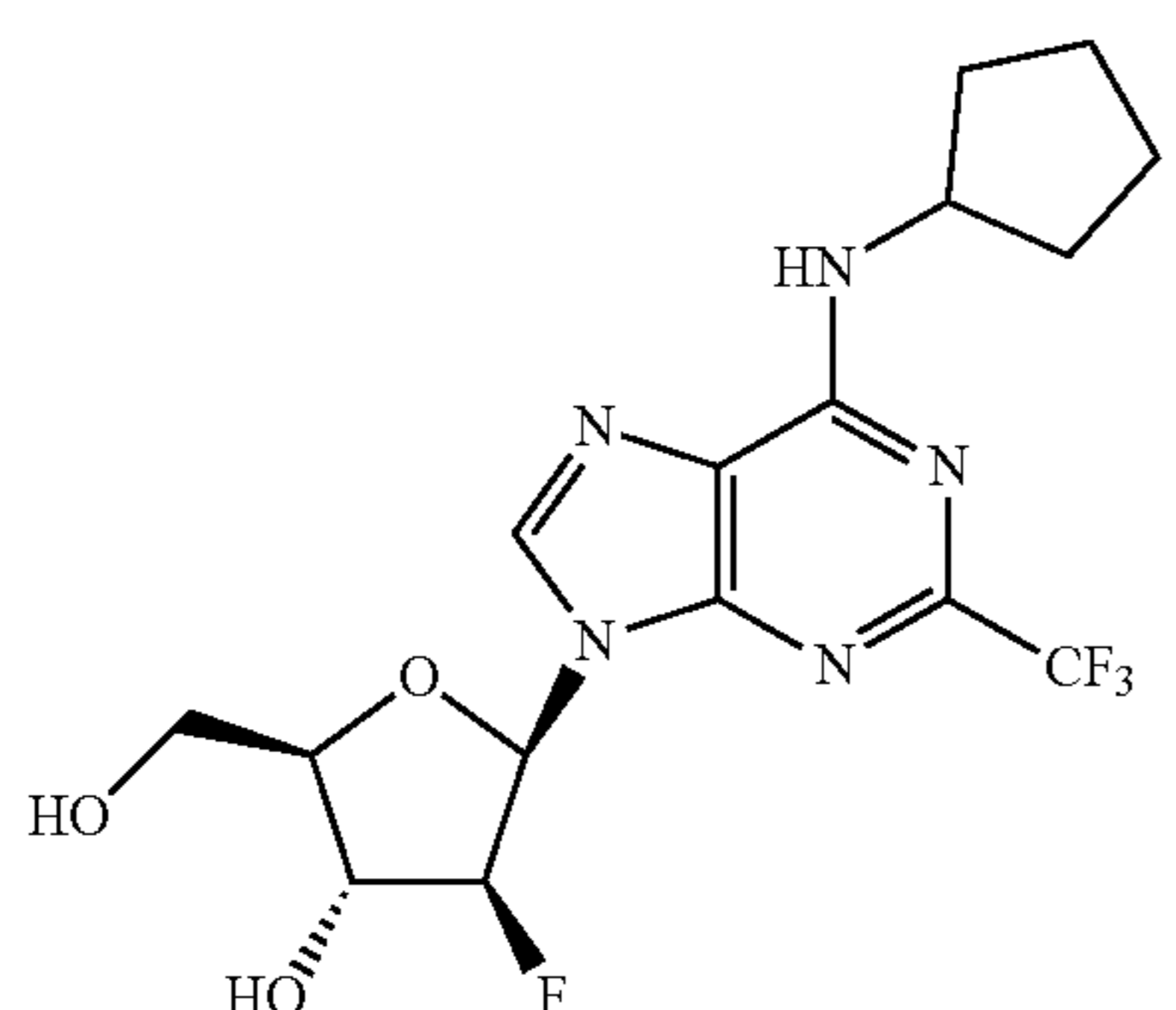
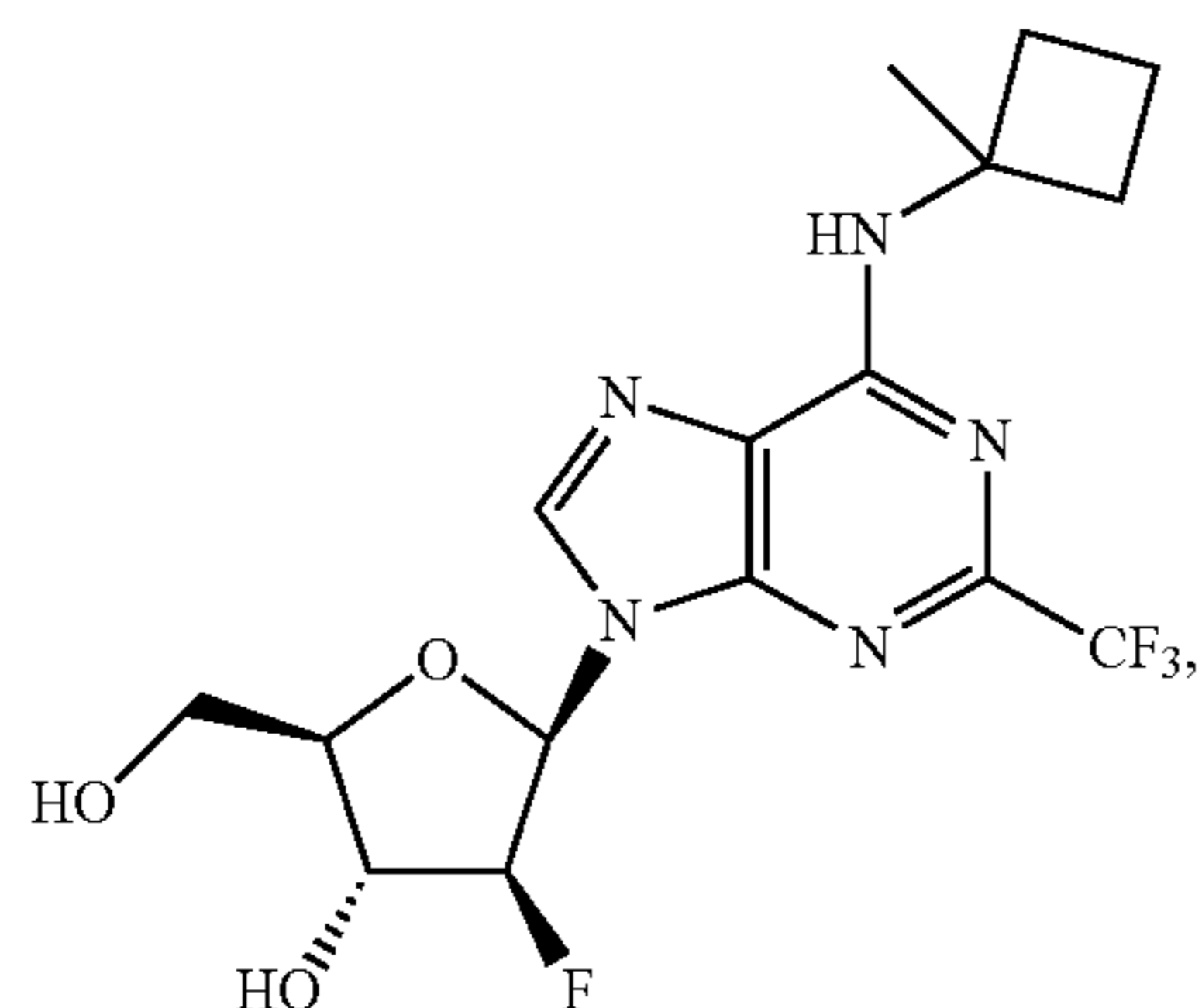
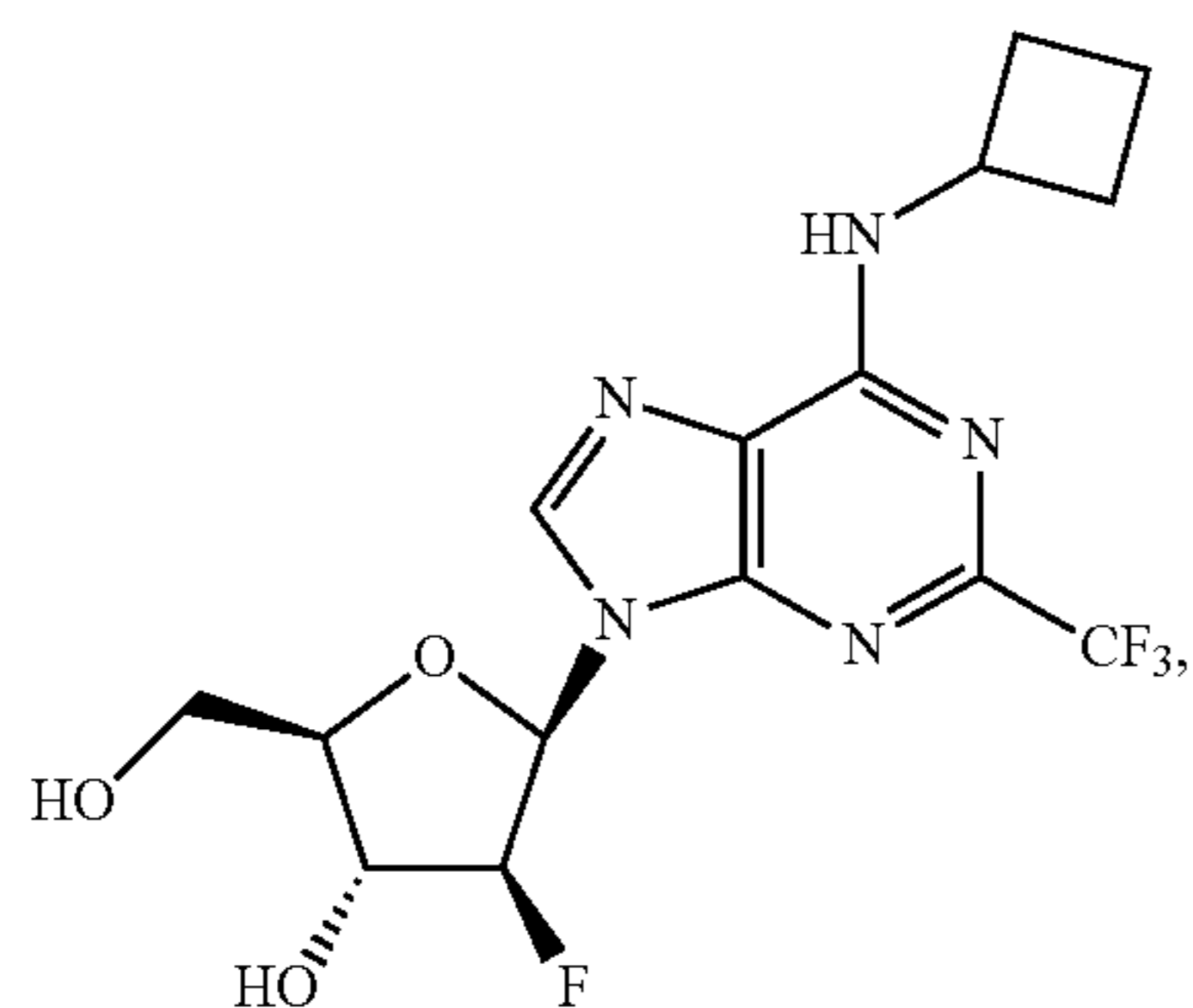
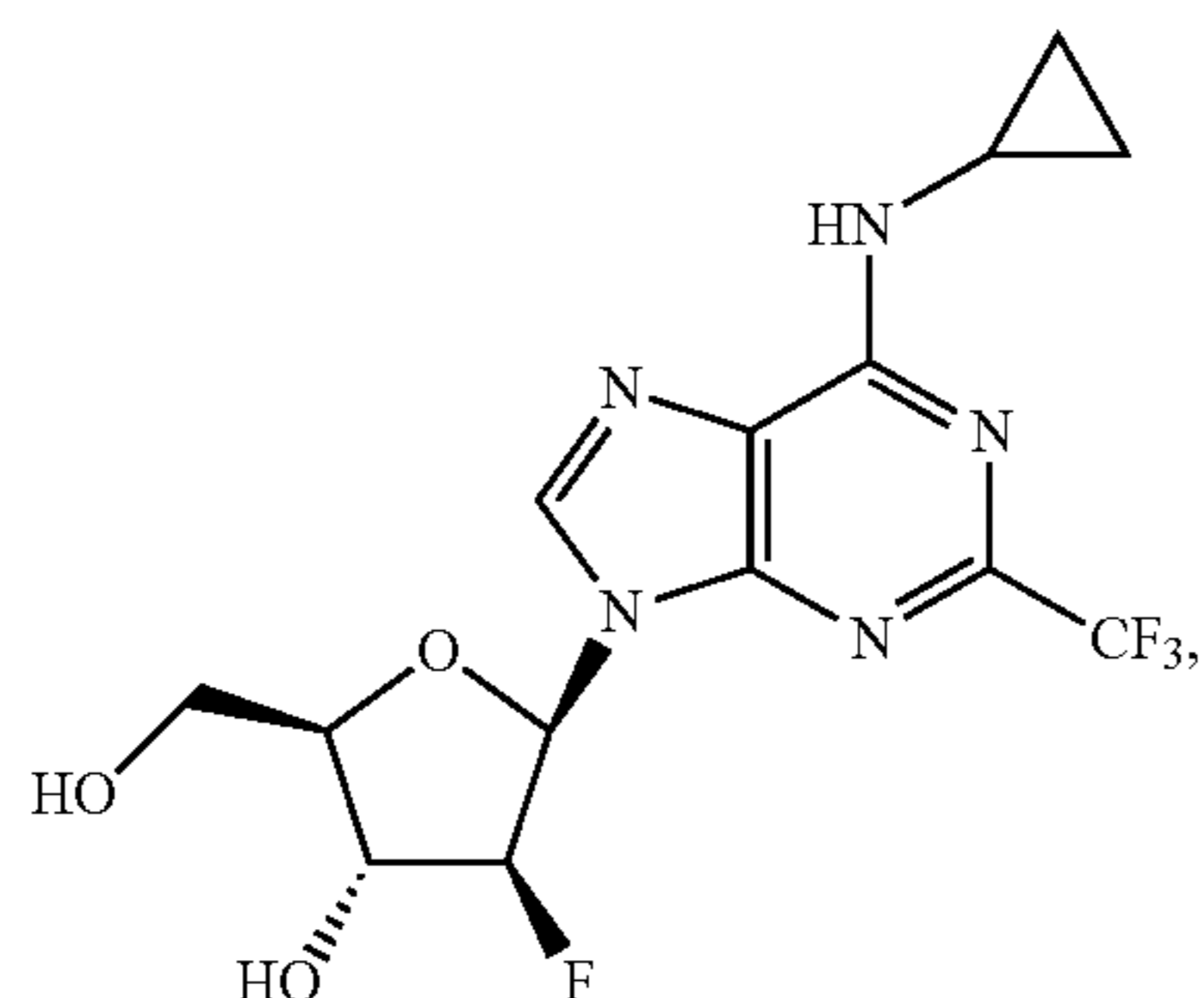
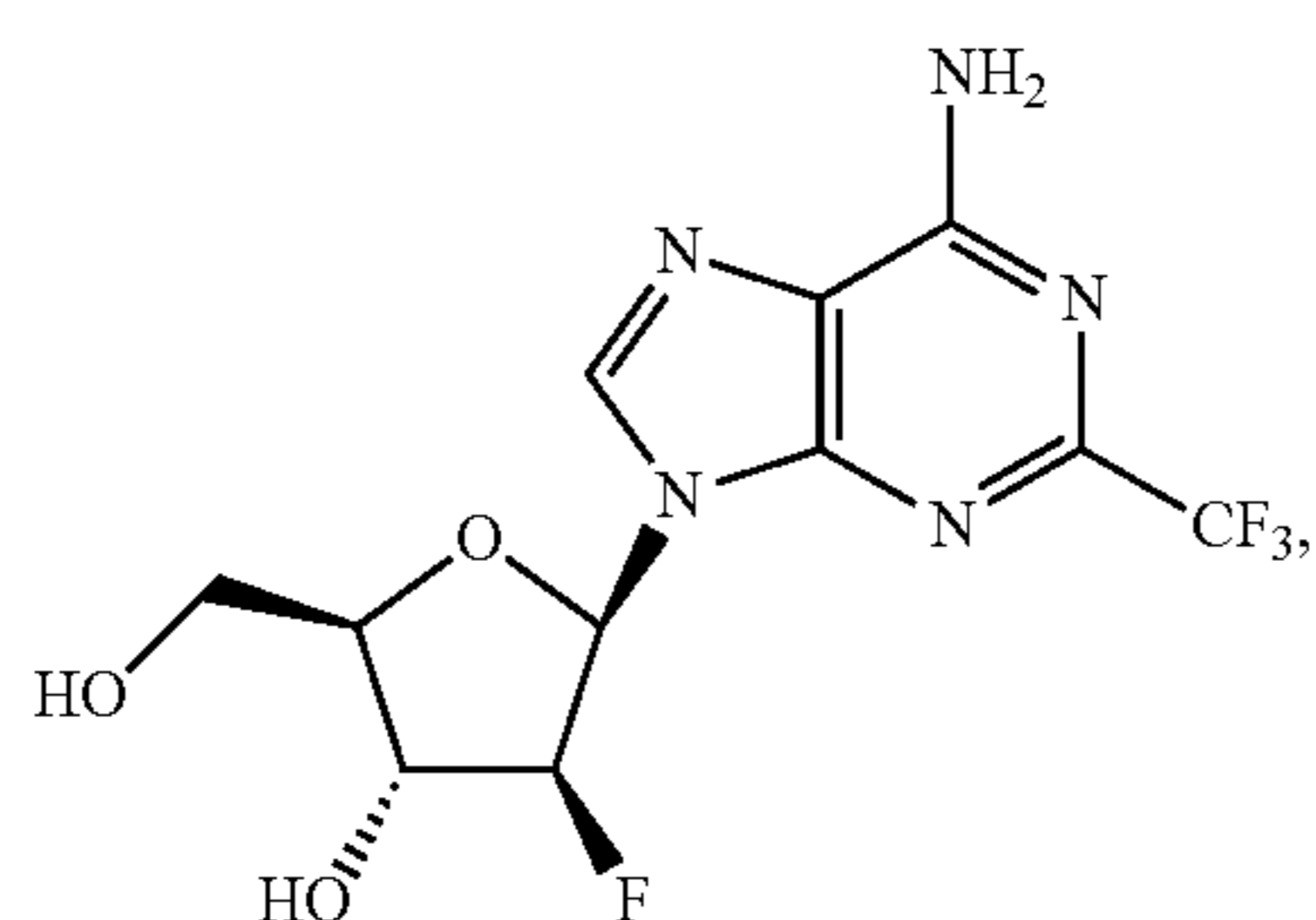
cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-\text{OH}$, C1-C12 alkyl, C1-C12 alkoxy, $-C(O)R^{14}$, $-(\text{C1-C12 alkyl})\text{CO}_2\text{H}$, and $-(\text{C1-C6 alkyl})\text{Cy}^2$; wherein R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)\text{R}^{21}$; wherein R^{21} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8 alkyl})\text{CO}_2\text{H}$, $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^3 , and $-(\text{C1-C8 alkyl})\text{Cy}^3$; wherein Cy^3 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy^2 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine, provided that when each of R^1 , R^2 , R^{3a} , and R^{3b} are not simultaneously hydrogen, and provided that when each of R^1 , R^2 , and R^{3a} is hydrogen then R^{3b} is not $-\text{CH}_2(\text{unsubstituted cyclohexyl})$, or a pharmaceutically acceptable salt thereof, thereby treating cancer in the subject.

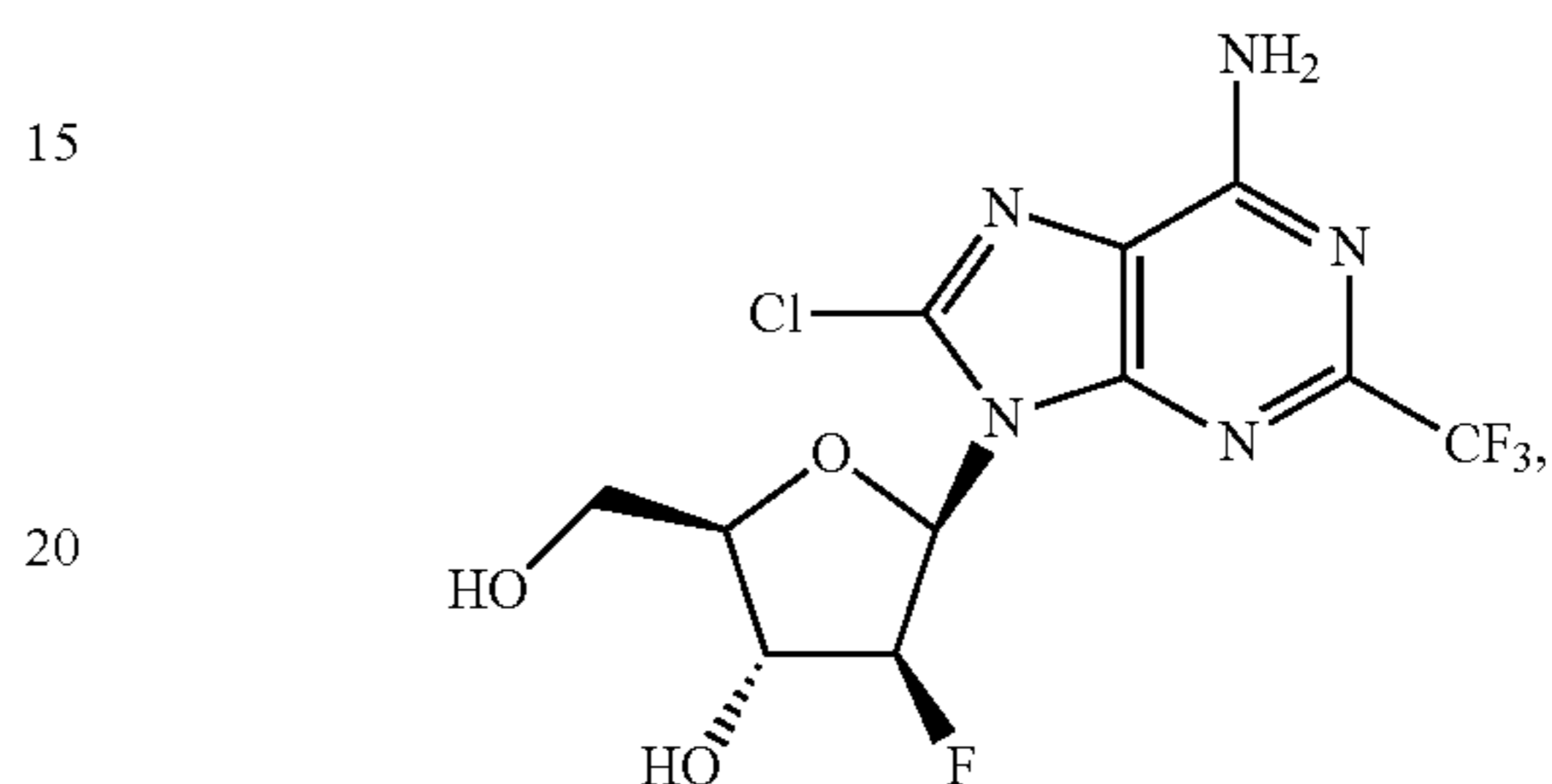
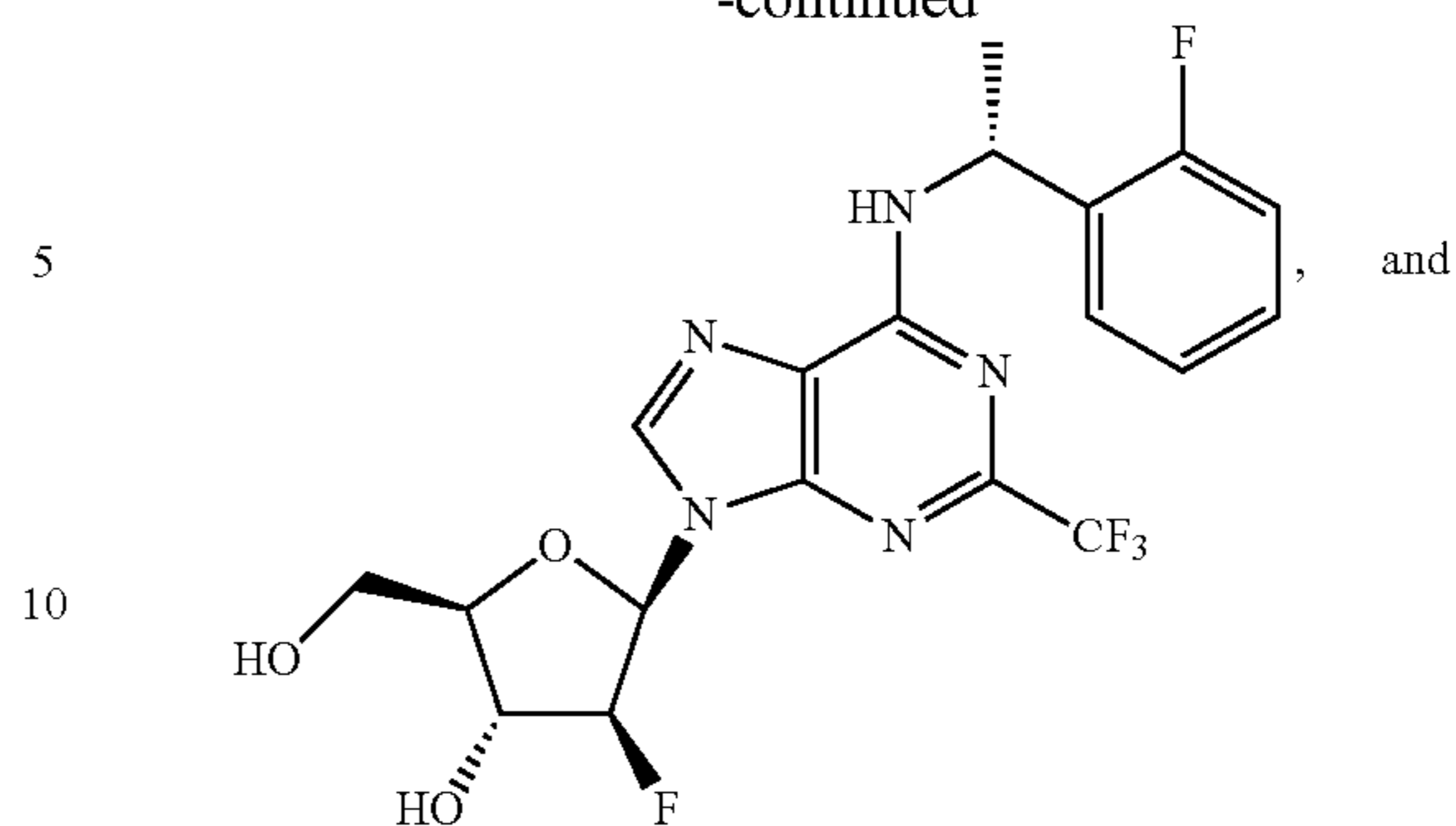
In one aspect, disclosed are methods of treating cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound having a structure selected from:

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-continued



25 or a pharmaceutically acceptable salt thereof, thereby treating cancer in the subject.

Examples of cancers include, but are not limited to, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

In a further aspect, the subject has been diagnosed with a need for treatment of cancer prior to the administering step.

30 In a further aspect, the subject is a mammal. In a still further aspect, the mammal is a human.

In various aspects, the method further comprises the step of identifying a subject in need of treatment of cancer. In a further aspect, the cancer is selected from a sarcoma, a carcinoma, a hematological cancer, a solid tumor, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanoma, glioma, leukemia, lymphoma, chronic myeloproliferative disorder, myelodysplastic syndrome, myeloproliferative neoplasm, and plasma cell neoplasm (myeloma). In yet a further aspect, the cancer is a solid tumor. In an even further aspect, the cancer is breast cancer.

45 In a further aspect, the effective amount is a therapeutically effective amount.

50 In a still further aspect, the effective amount is a prophylactically effective amount.

In a further aspect, the method further comprises the step of administering a therapeutically effective amount of at least one agent associated with the treatment of cancer. In a still further aspect, the at least one agent is a chemotherapeutic agent. In yet a further aspect, the chemotherapeutic agent is selected from an alkylating agent, an antimetabolite agent, an antineoplastic antibiotic agent, a mitotic inhibitor agent, and a mTor inhibitor agent. In an even further aspect, the at least one agent is a chemotherapeutic agent or an anti-neoplastic agent. In a still further aspect, the chemo-

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therapeutic agent or anti-neoplastic agent is selected from kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors and other DNA damage response modifiers, epigenetic agents such as bromodomain and extra-terminal (BET) inhibitors, histone deacetylase (HDAC) inhibitors, iron chelators and other ribonucleotides reductase inhibitors, proteasome inhibitors and Nedd8-activating enzyme (NAE) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, traditional cytotoxic agents such as paclitaxel, dox, irinotecan, and platinum compounds, immune checkpoint blockade agents such as cytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody (mAB), programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) mAB, cluster of differentiation 47 (CD47) mAB, toll-like receptor (TLR) agonists and other immune modifiers, cell therapeutics such as chimeric antigen receptor T-cell (CAR-T)/chimeric antigen receptor natural killer (CAR-NK) cells, and proteins such as interferons (IFNs), interleukins (ILs), and mAbs.

In a further aspect, the antineoplastic antibiotic agent is selected from doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, pliamycin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt thereof.

In a further aspect, the antimetabolite agent is selected from gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt thereof.

In a further aspect, the alkylating agent is selected from carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt thereof.

In a further aspect, the mitotic inhibitor agent is selected from irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etoposide, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt thereof.

In a further aspect, the mTor inhibitor agent is selected from everolimus, sirolimus, and temsirolimus, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

In a further aspect, the kinase inhibitor is selected from p38 inhibitors, CDK inhibitors, TNF inhibitors, matrixmetalloproteinase (MMP) inhibitors, COX-2 inhibitors, including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, SOD mimics, and α,β -inhibitors.

In a further aspect, the PARP inhibitor is selected from iniparib, talazoparib, olaparib, rucapariv, veliparib, CEP 9722, AK 4827, BGB-290 and 3-aminobenzamide.

In a further aspect, the epigenetic agent is selected from a histone deacetylase inhibitor and a DNA methylation inhibitor. In a still further aspect, the epigenetic agent is a BET inhibitor. In yet a further aspect, the BET inhibitor is selected from JQ1, 1-BET 151 (GSK1210151A), I-BET 762 (GSK525762), OTX-015, TEN-010 (Tensha therapeutics), CPI-203, RVX-208 (Resverlogix Corp), LY294002, MK-8628 (Merck/Mitsubishi Tanabe), BMS-986158 (Bristol-Myers Squibb), INCB54329 (Incyte Pharmaceuticals), ABBV-075 (Abb Vie, also called ABV-075), CPI-0610 (Constellation Pharmaceuticals/Roche), FT-1101 (Forma Therapeutics/Celgene), GS-5829 (Gilead Sciences), and PLX51107 (Daiichi Sankyo).

In a further aspect, the HDAC inhibitor is selected from pracinostat and panobinostat.

In a further aspect, the ribonucleotide reductase inhibitor is selected from fludarabine, cladribine, gemcitabine, tezacitabine, triapine, motexafin gadolinium, hydroxyurea, gallium maltolate, and gallium nitrate. In a still further aspect, the ribonucleotide reductase inhibitor is an iron chelator.

In a further aspect, the proteasome inhibitor is selected from lactacystin and bortezomib.

In a further aspect, the NAE inhibitor is a 1-substituted methyl sulfamate. In a still further aspect, the NAE inhibitor is MLN4924.

In a further aspect, the immune checkpoint blockade agent is selected from anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-LAG3 antibodies, anti-B7-H3 antibodies, anti-TEVI3 antibodies, antibodies to PD-1, CTLA-4, BTLA, TIM-3, LAG-3, CD160, TIGIT, LAIR1, and 2B4, antibodies to the corresponding ligands for these receptors including, but not limited to, PD-L1 (for PD-1), PD-L2 (for PD-1), CD80 and CD86 (for CTLA-4), HVEM (for BTLA), Galectin-9 and HMGB1 (for TIM-3), MHC II (for LAG-3), HVEM (for CD160), CD155, CD112, and CD113 (for TIGIT), C1q and collagen (for LAIR1), and CD48 (for 2B4). In a still further aspect, the immune checkpoint blockade agent is selected from CTL-4 mAb, PD-1/PD-L1 mAB, and CD47 mAB.

In a further aspect, the TLR agonist is selected from CRX-527 and OM-174.

In a further aspect, the cell therapeutic is selected from CAR-T cell therapy and CAR-NK cell therapy.

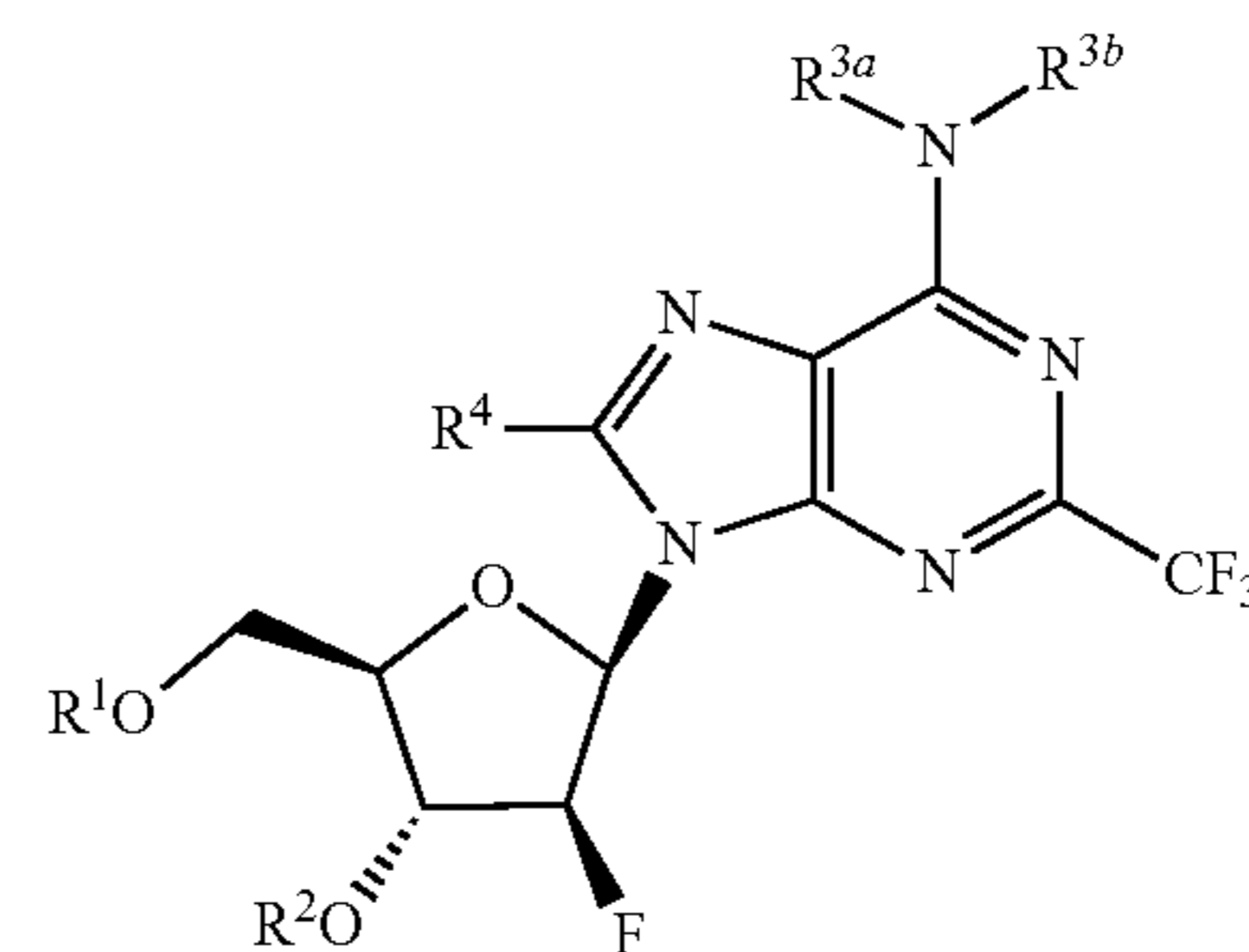
In a further aspect, the compound and the agent are administered sequentially. In a still further aspect, the compound and the agent are administered simultaneously.

In a further aspect, the compound and the agent are co-formulated. In a still further aspect, the compound and the agent are co-packaged.

F. Methods of Modifying Nucleic Acid Synthesis in a Subject

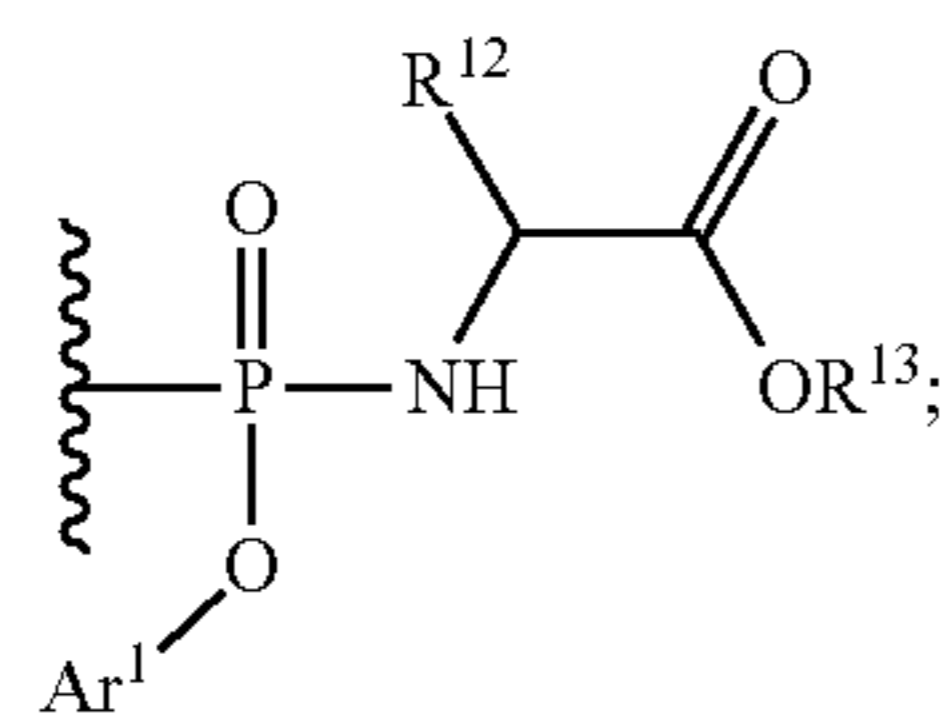
In one aspect, disclosed are methods of modifying nucleic acid synthesis in a subject, the method comprising the step of administering to the subject an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

Thus, in one aspect, disclosed are methods of modifying nucleic acid synthesis in a subject, the method comprising administering to the subject an effective amount of a compound having a structure represented by a formula:

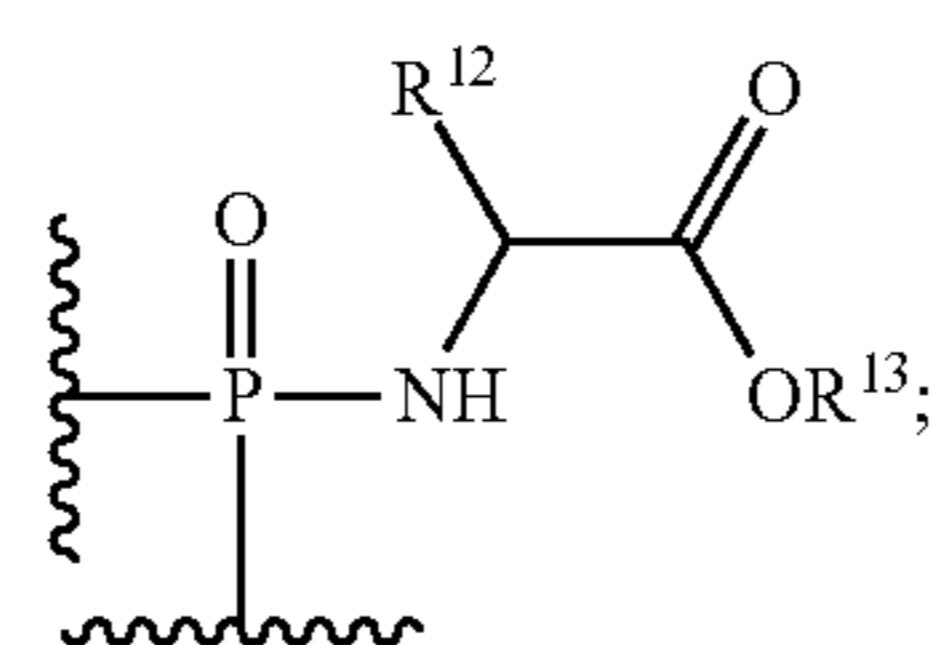


wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:

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wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)\text{R}^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8 alkyl})\text{CO}_2\text{H}$, $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^1 , and $-(\text{C1-C8 alkyl})\text{Cy}^1$; wherein Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkyl})$, $-(\text{C1-C10 alkyl})\text{CO}_2(\text{C1-C10 alkylthiol})$, $-(\text{C1-C10 alkyl})\text{S}-\text{S}-(\text{C1-C10 alkyl})$, and Ar^2 ; wherein Ar^2 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:

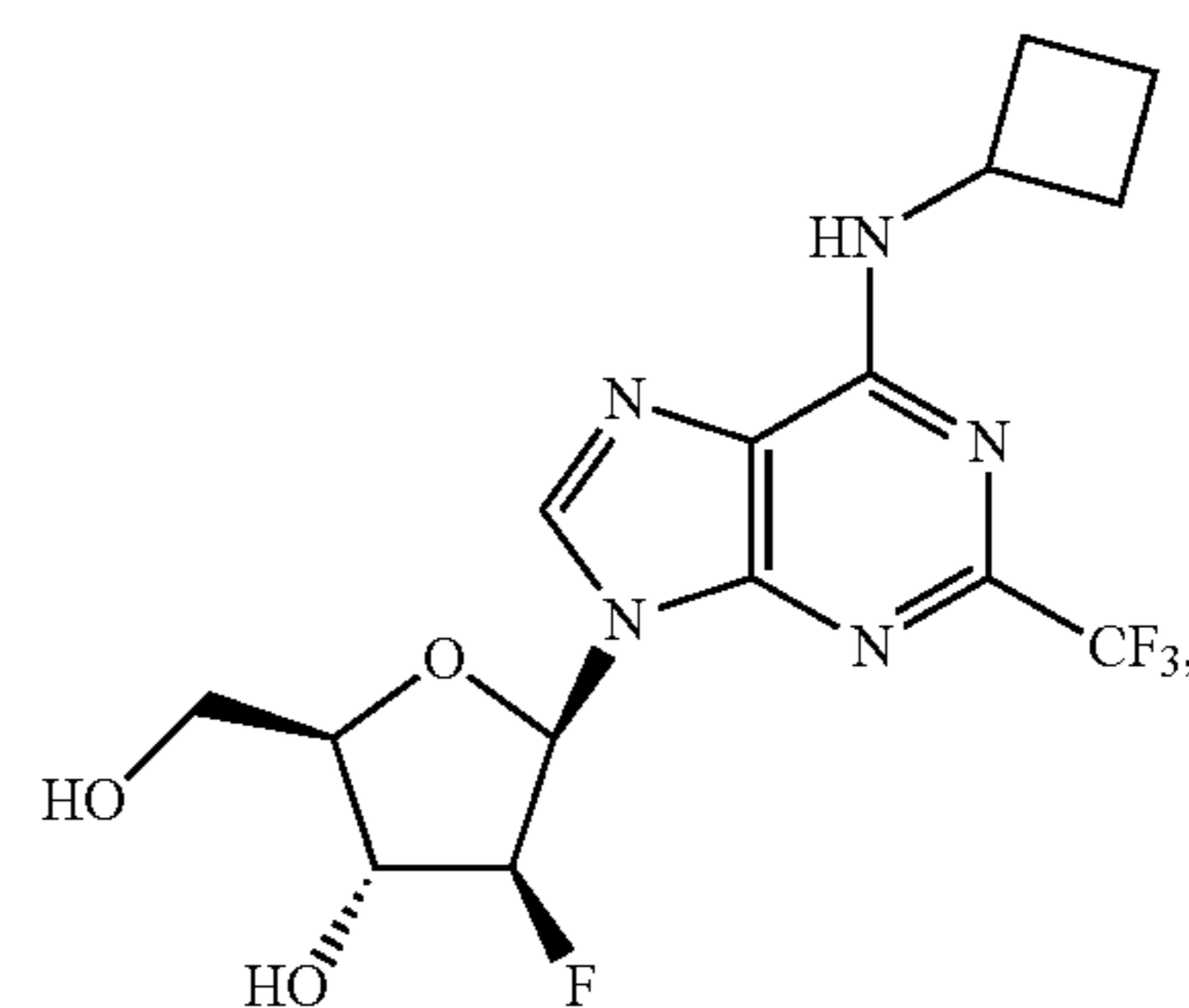
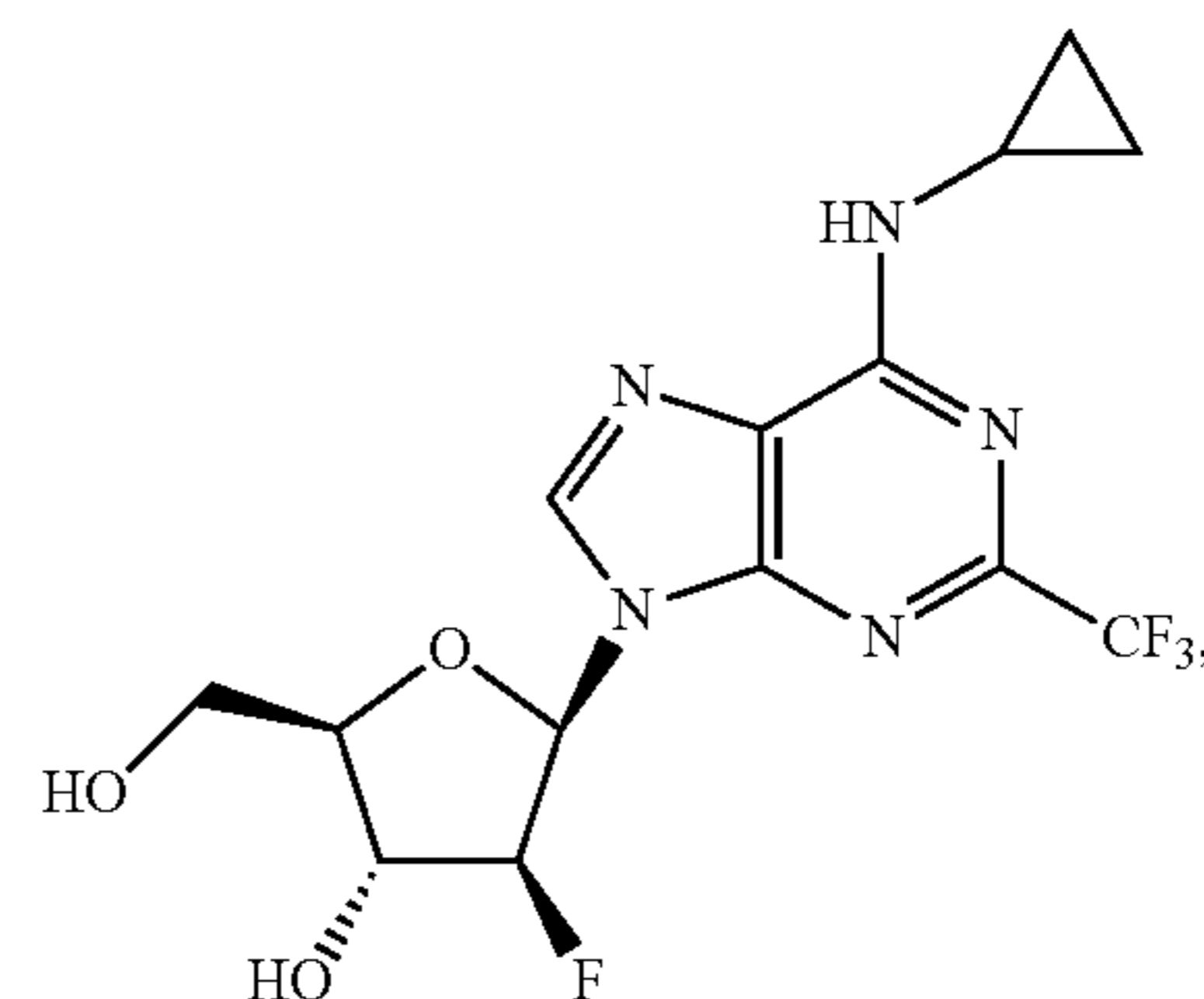
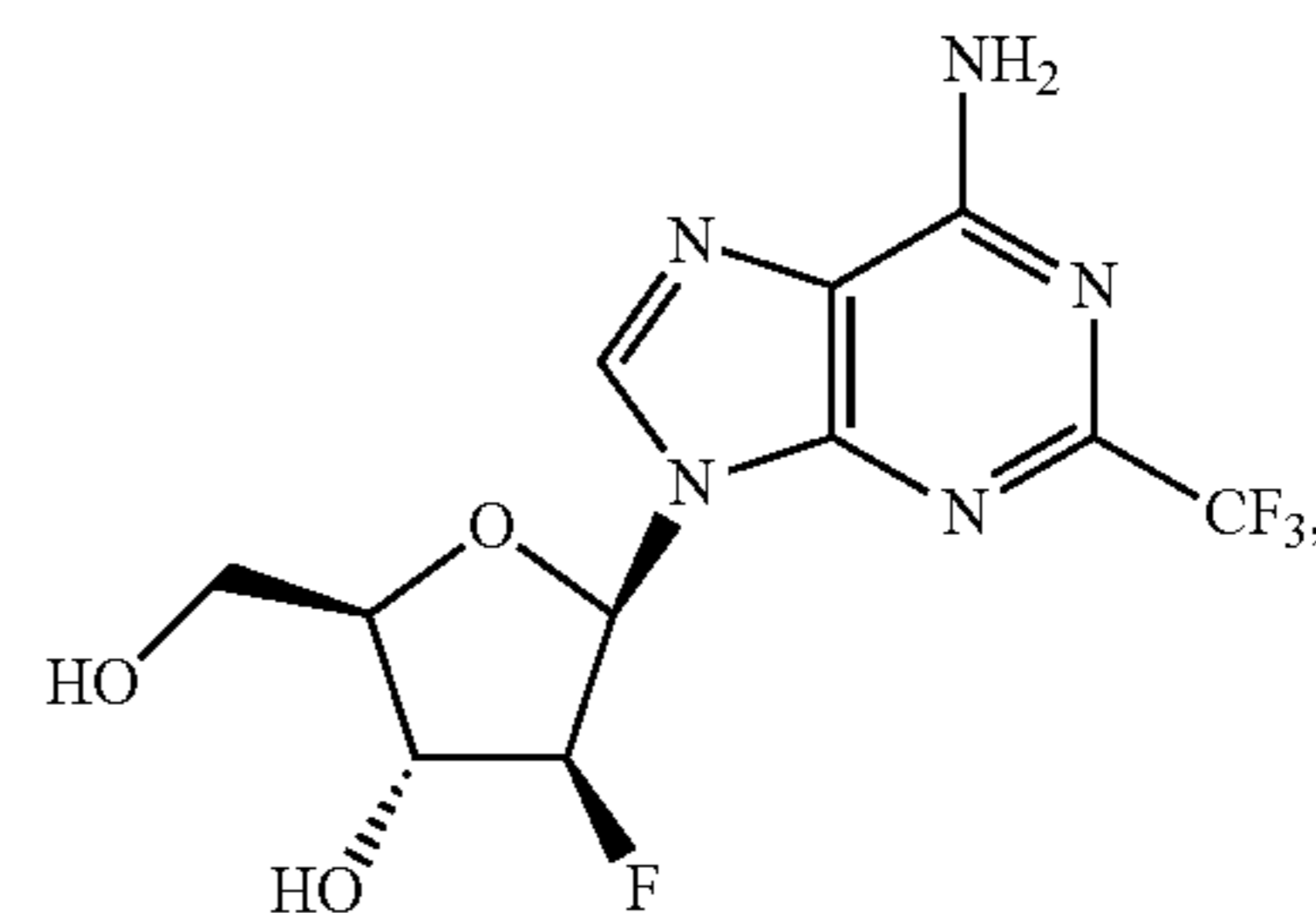


wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, $-\text{OH}$, C1-C12 alkyl, C1-C12 alkoxy, $-\text{C}(\text{O})\text{R}^{14}$, $-(\text{C1-C12 alkyl})\text{CO}_2\text{H}$, and $-(\text{C1-C6 alkyl})\text{Cy}^2$; wherein R^{14} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-\text{CH}(\text{NH}_2)\text{R}^{20}$; wherein R^{21} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8

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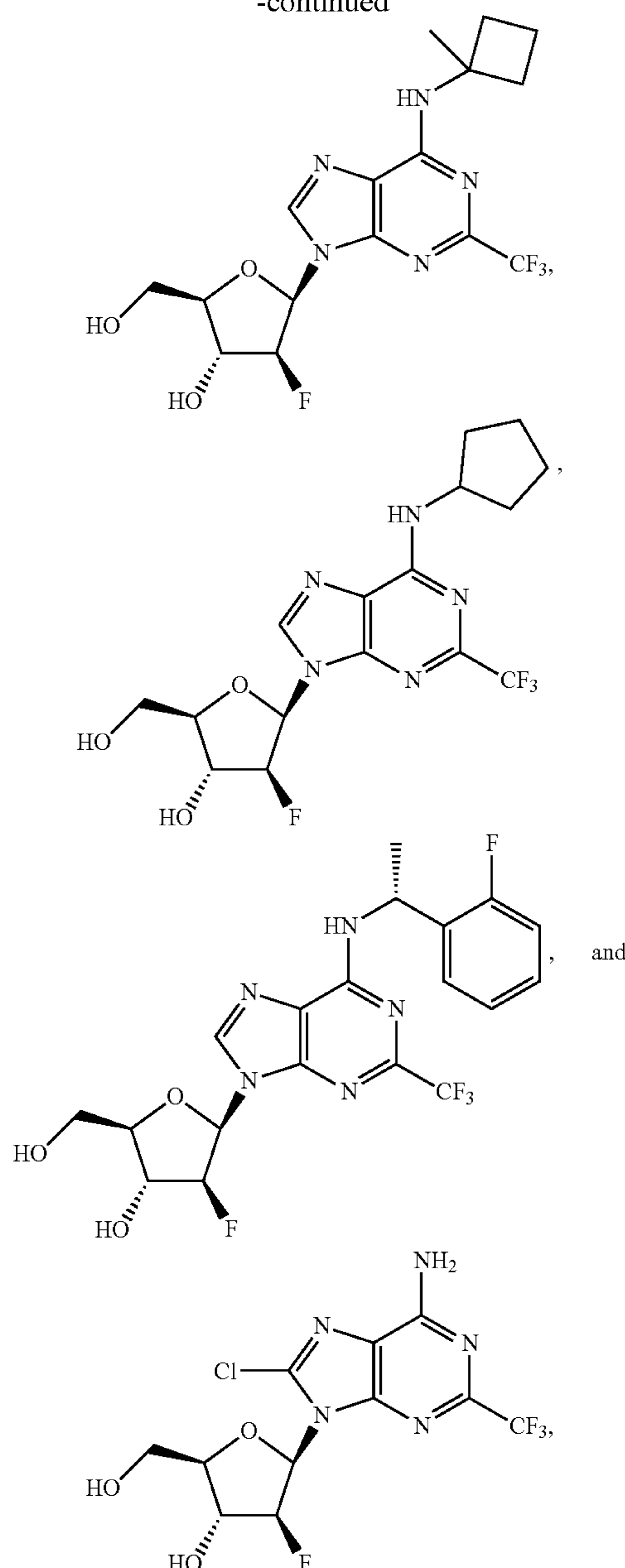
hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(\text{C1-C8 alkyl})\text{NHC}(\text{NH})\text{NH}_2$, $-(\text{C1-C8 alkyl})\text{CO}_2\text{H}$, $-(\text{C1-C8 alkyl})\text{C}(\text{O})\text{NH}_2$, Cy^3 , and $-(\text{C1-C8 alkyl})\text{Cy}^3$; wherein Cy^3 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy^2 , when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NO}_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R^4 is hydrogen or chlorine, provided that when each of R^1 , R^2 , R^{3a} , and R^{3b} are not simultaneously hydrogen, and provided that when each of R^1 , R^2 , and R^{3a} is hydrogen then R^{3b} is not $-\text{CH}_2(\text{unsubstituted cyclohexyl})$, or a pharmaceutically acceptable salt thereof, thereby modifying nucleic acid synthesis in the subject.

In one aspect, disclosed are methods of modifying nucleic acid synthesis in a subject, the method comprising administering to the subject an effective amount of a compound having a structure selected from:



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-continued



or a pharmaceutically acceptable salt thereof, thereby modifying nucleic acid synthesis in the subject.

In various aspects, modifying is inhibiting. In a further aspect, modifying is decreasing.

In various aspects, the nucleic acid is deoxyribonucleic acid (DNA). In a further aspect, the nucleic acid is ribonucleic acid (RNA). In a still further aspect, the nucleic acid is a combination of DNA and RNA.

In various aspects, the subject has been diagnosed with cancer prior to the administering step. Examples of cancers include, but are not limited to, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

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In a further aspect, the subject has been diagnosed with a need for modifying nucleic acid synthesis prior to the administering step.

In a further aspect, the subject is a mammal. In a still further aspect, the mammal is a human.

In various aspects, the method further comprises the step of identifying a subject in need of treatment of cancer. In a further aspect, the cancer is selected from a sarcoma, a carcinoma, a hematological cancer, a solid tumor, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanoma, glioma, leukemia, lymphoma, chronic myeloproliferative disorder, myelodysplastic syndrome, myeloproliferative neoplasm, and plasma cell neoplasm (myeloma). In yet a further aspect, the cancer is a solid tumor. In an even further aspect, the cancer is breast cancer.

In a further aspect, the effective amount is a therapeutically effective amount. In a still further aspect, the effective amount is a prophylactically effective amount.

In a further aspect, the method further comprises the step of administering a therapeutically effective amount of at least one agent associated with the treatment of cancer. In a still further aspect, the at least one agent is a chemotherapeutic agent. In yet a further aspect, the chemotherapeutic agent is selected from an alkylating agent, an antimetabolite agent, an antineoplastic antibiotic agent, a mitotic inhibitor agent, and a mTor inhibitor agent. In an even further aspect, the at least one agent is a chemotherapeutic agent or an anti-neoplastic agent. In a still further aspect, the chemotherapeutic agent or anti-neoplastic agent is selected from kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors and other DNA damage response modifiers, epigenetic agents such as bromodomain and extra-terminal (BET) inhibitors, histone deacetylase (HDAC) inhibitors, iron chelators and other ribonucleotides reductase inhibitors, proteasome inhibitors and Nedd8-activating enzyme (NAE) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, traditional cytotoxic agents such as paclitaxel, dox, irinotecan, and platinum compounds, immune checkpoint blockade agents such as cytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody (mAB), programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) mAB, cluster of differentiation 47 (CD47) mAB, toll-like receptor (TLR) agonists and other immune modifiers, cell therapeutics such as chimeric antigen receptor T-cell (CAR-T)/chimeric antigen receptor natural killer (CAR-NK) cells, and proteins such as interferons (IFNs), interleukins (ILs), and mAbs.

In a further aspect, the antineoplastic antibiotic agent is selected from doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plinacanthin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt thereof.

In a further aspect, the antimetabolite agent is selected from gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt thereof.

In a further aspect, the alkylating agent is selected from carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt thereof.

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In a further aspect, the mitotic inhibitor agent is selected from irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etoposide, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt thereof.

In a further aspect, the mTor inhibitor agent is selected from everolimus, sirolimus, and temsirolimus, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

In a further aspect, the kinase inhibitor is selected from p38 inhibitors, CDK inhibitors, TNF inhibitors, matrix metallo proteinase (MMP) inhibitors, COX-2 inhibitors, including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, SOD mimics, and avP3-inhibitors.

In a further aspect, the PARP inhibitor is selected from iniparib, talazoparib, olaparib, rucapariv, veliparib, CEP 9722, AK 4827, BGB-290 and 3-aminobenzamide.

In a further aspect, the epigenetic agent is selected from a histone deacetylase inhibitor and a DNA methylation inhibitor. In a still further aspect, the epigenetic agent is a BET inhibitor. In yet a further aspect, the BET inhibitor is selected from JQ1, 1-BET 151 (GSK1210151A), I-BET 762 (GSK525762), OTX-015, TEN-010 (Tensha therapeutics), CPI-203, RVX-208 (Resverlogix Corp), LY294002, MK-8628 (Merck/Mitsubishi Tanabe), BMS-986158 (Bristol-Myers Squibb), INCB54329 (Incyte Pharmaceuticals), ABBV-075 (Abb Vie, also called ABV-075), CPI-0610 (Constellation Pharmaceuticals/Roche), FT-1101 (Forma Therapeutics/Celgene), GS-5829 (Gilead Sciences), and PLX51107 (Daiichi Sankyo).

In a further aspect, the HDAC inhibitor is selected from pracinostat and panobinostat.

In a further aspect, the ribonucleotide reductase inhibitor is selected from fludarabine, cladribine, gemcitabine, tezacitabine, triapine, motexafin gadolinium, hydroxyurea, gallium maltolate, and gallium nitrate. In a still further aspect, the ribonucleotide reductase inhibitor is an iron chelator.

In a further aspect, the proteasome inhibitor is selected from lactacystin and bortezomib.

In a further aspect, the NAE inhibitor is a 1-substituted methyl sulfamate. In a still further aspect, the NAE inhibitor is MLN4924.

In a further aspect, the immune checkpoint blockade agent is selected from anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-LAG3 antibodies, anti-B7-H3 antibodies, anti-TEVI3 antibodies, antibodies to PD-1, CTLA-4, BTLA, TIM-3, LAG-3, CD160, TIGIT, LAIR1, and 2B4, antibodies to the corresponding ligands for these receptors including, but not limited to, PD-L1 (for PD-1), PD-L2 (for PD-1), CD80 and CD86 (for CTLA-4), HVEM (for BTLA), Galectin-9 and HMGB1 (for TIM-3), MHC II (for LAG-3), HVEM (for CD160), CD155, CD112, and CD113 (for TIGIT), Clq and collagen (for LAIR1), and CD48 (for 2B4). In a still further aspect, the immune checkpoint blockade agent is selected from CTL-4 mAb, PD-1/PD-L1 mAb, and CD47 mAb.

In a further aspect, the TLR agonist is selected from CRX-527 and OM-174.

In a further aspect the cell therapeutic is selected from CAR-T cell therapy and CAR-NK cell therapy.

In a further aspect, the compound and the agent are administered sequentially. In a still further aspect, the compound and the agent are administered simultaneously.

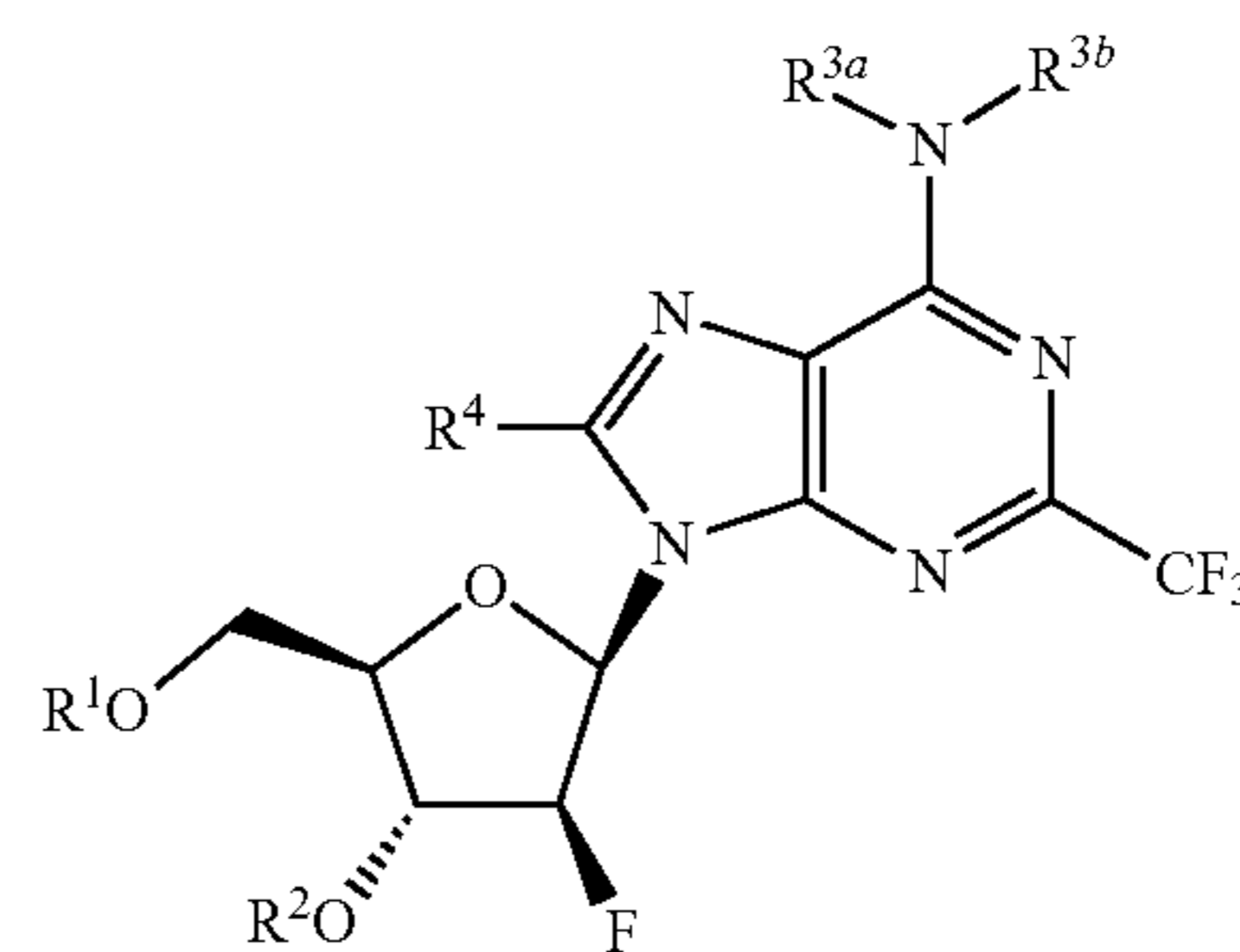
In a further aspect, the compound and the agent are co-formulated. In a still further aspect, the compound and the agent are co-packaged.

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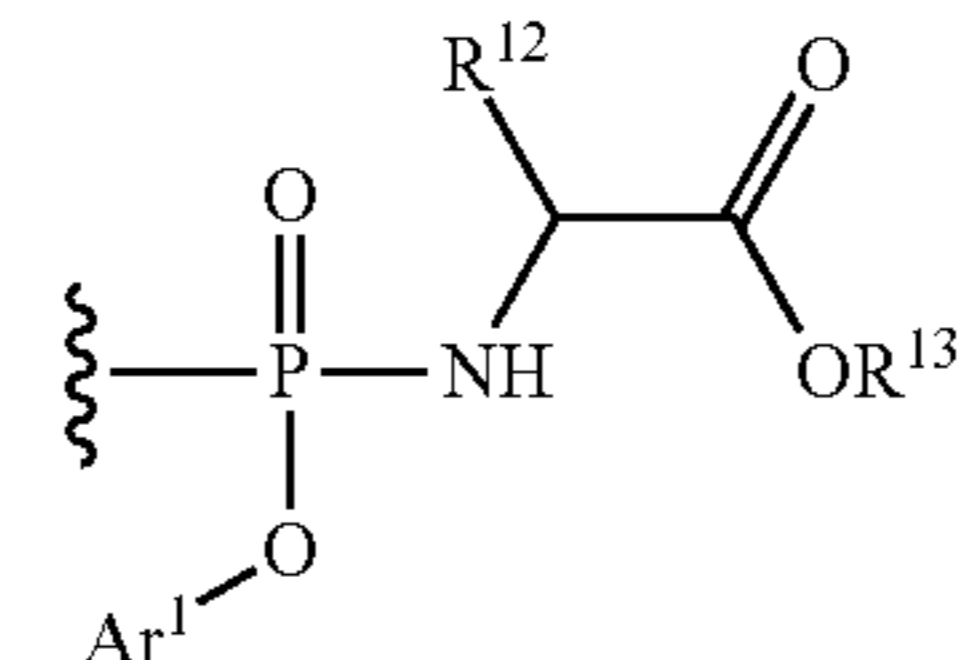
G. Methods of Modifying Nucleic Acid Synthesis in a Cell

In one aspect, disclosed are methods of modifying nucleic acid synthesis in a cell, the method comprising the step of contacting the cell with an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

Thus, in one aspect, disclosed are methods of modifying nucleic acid synthesis in a cell, the method comprising contacting the cell with an effective amount of a compound having a structure represented by a formula:



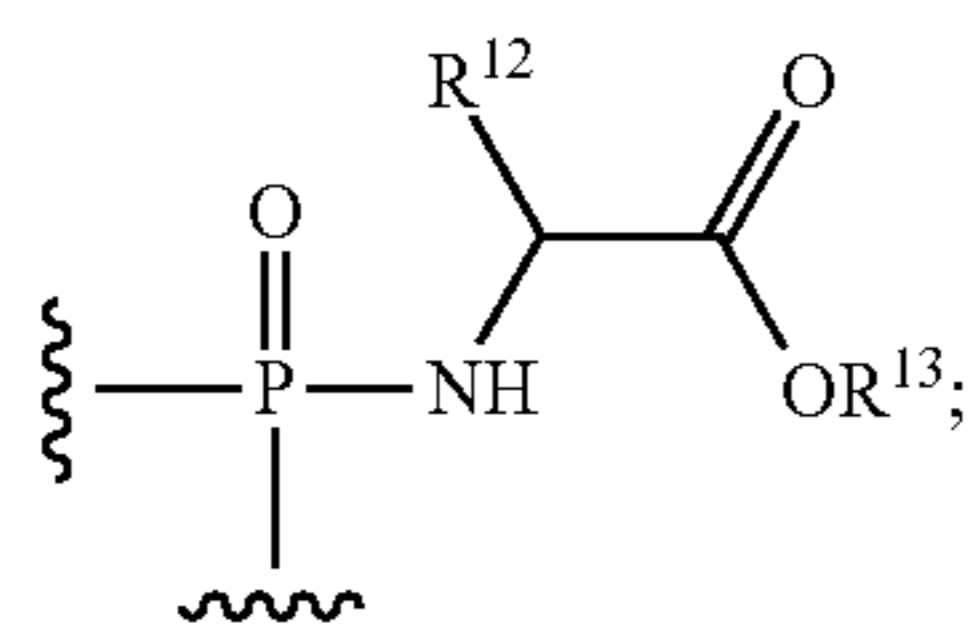
wherein one of R¹ and R² is hydrogen, and the other is selected from hydrogen, —C(O)R¹⁰, —P(O)(OR¹¹)₂, and a structure represented by a formula:



wherein R¹⁰, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH₂)R²⁰; wherein R²⁰, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, —(C1-C8 alkyl)NHC(NH)NH₂, —(C1-C8 alkyl)CO₂H, —(C1-C8 alkyl)C(O)NH₂, Cy¹, and —(C1-C8 alkyl)Cy¹; wherein Cy¹, when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R¹¹, when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, —(C1-C10 alkyl)CO₂(C1-C10 alkyl), —(C1-C10 alkyl)CO₂(C1-C10 alkylthiol), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar²; wherein Ar², when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R¹², when present, is selected from hydrogen and C1-C8 alkyl; wherein R¹³, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar³; wherein Ar³, when present, is selected

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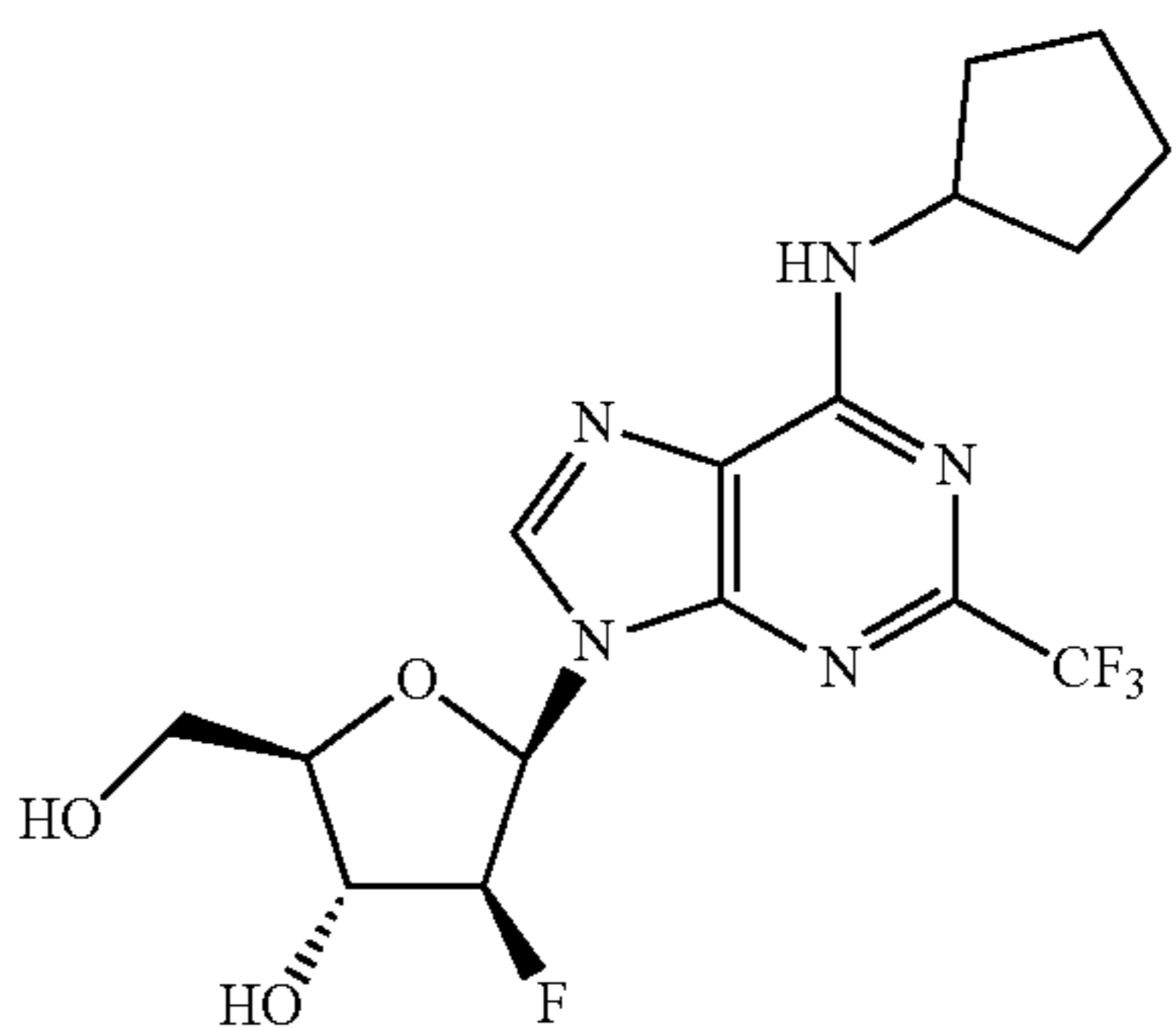
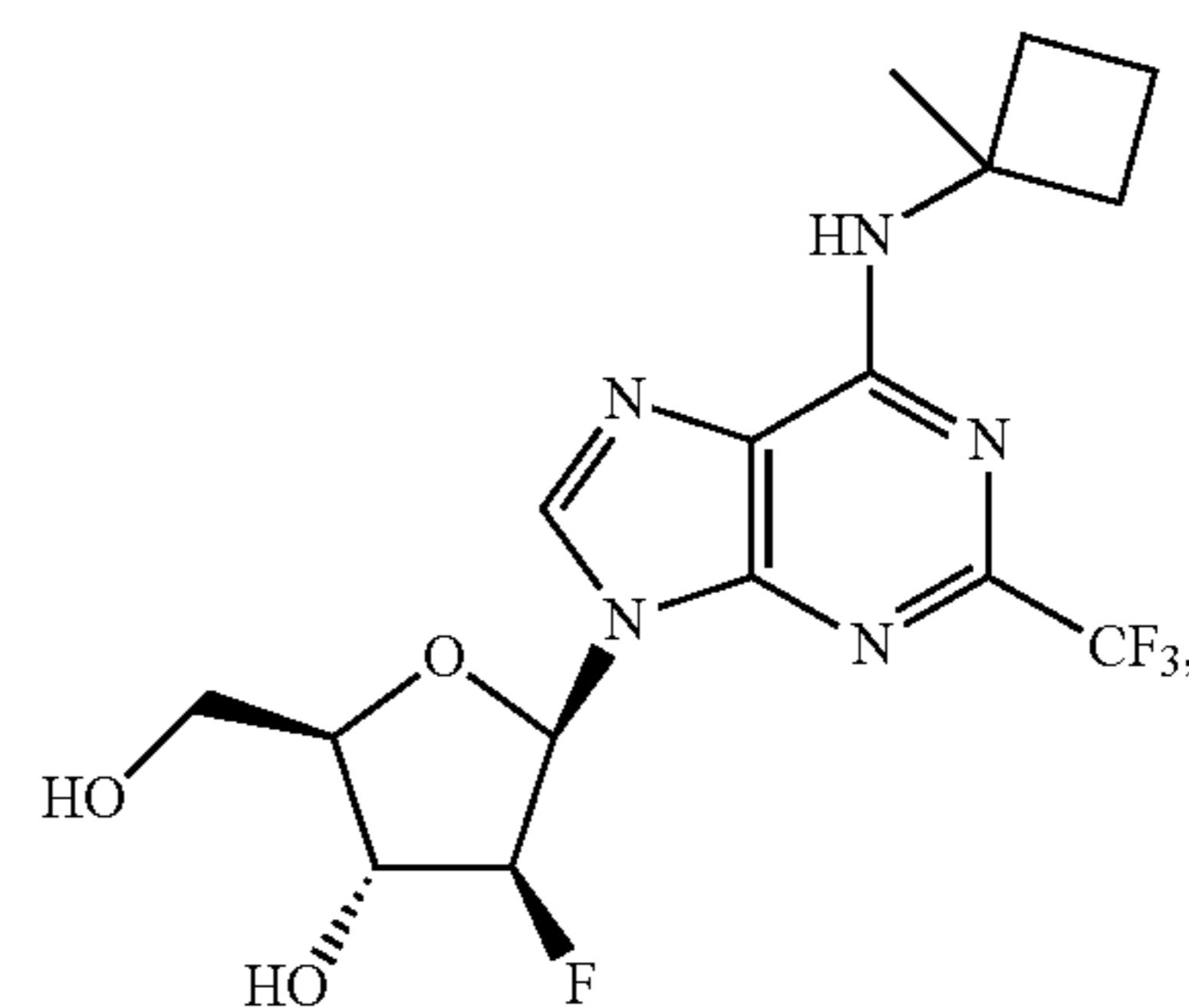
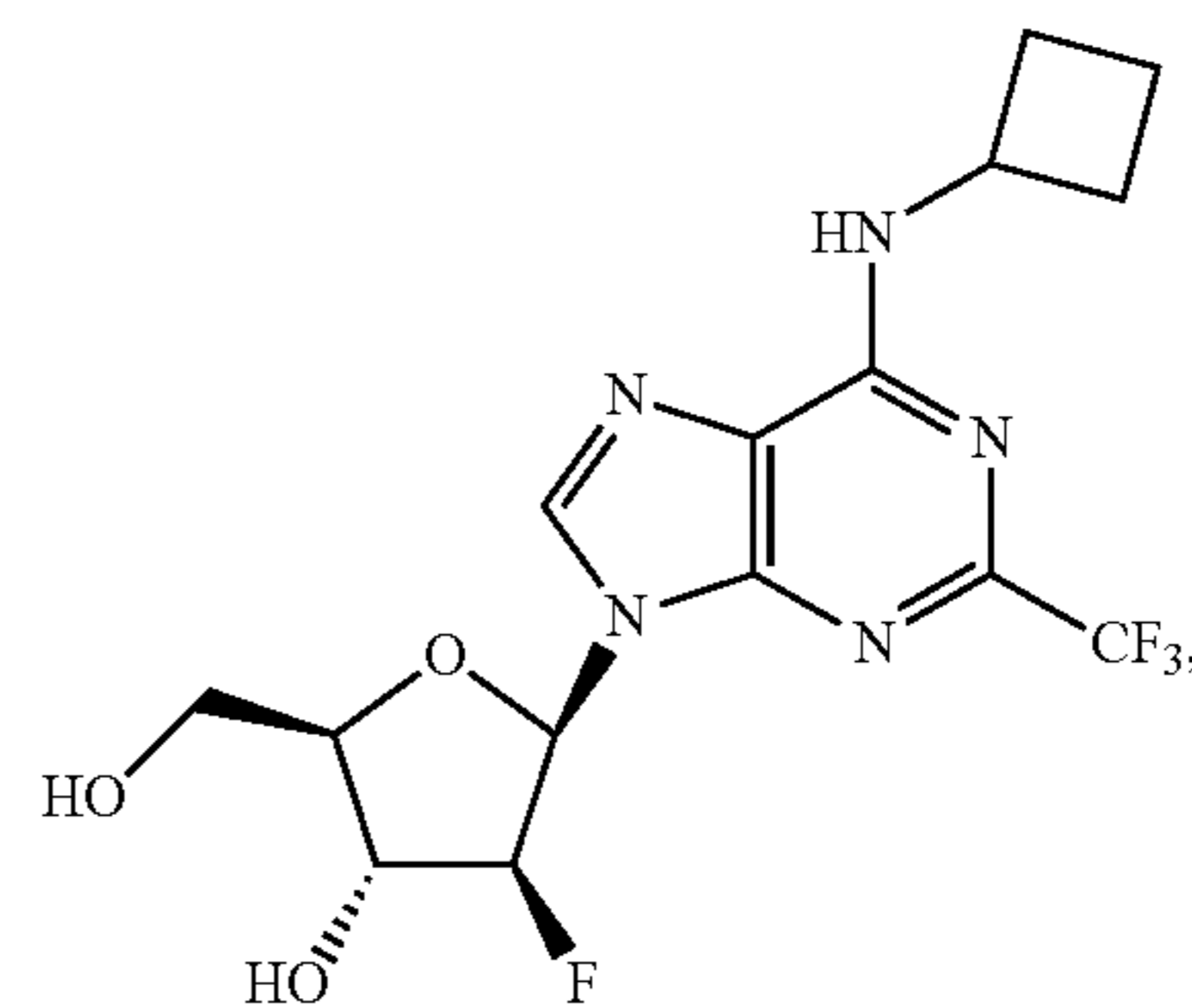
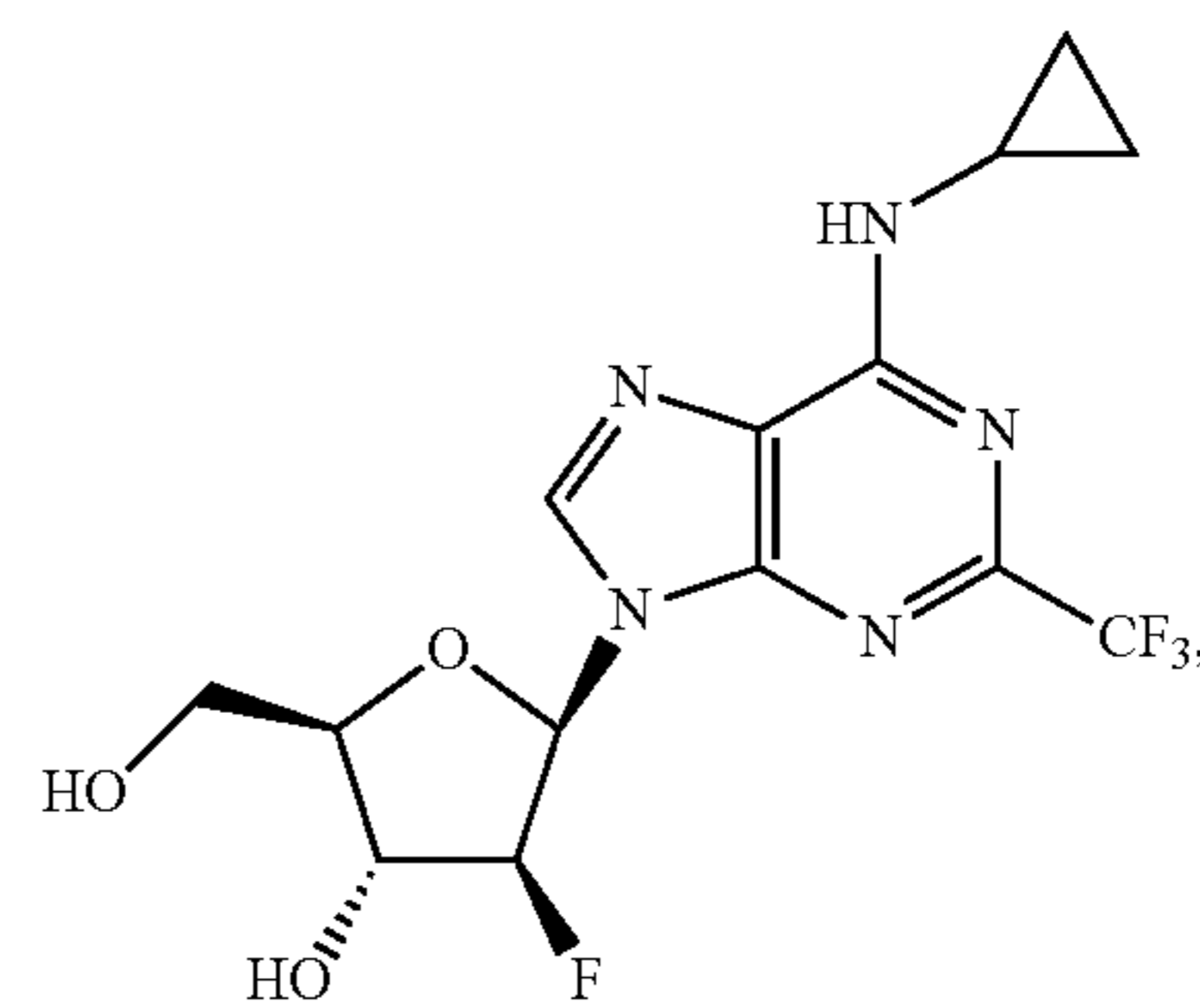
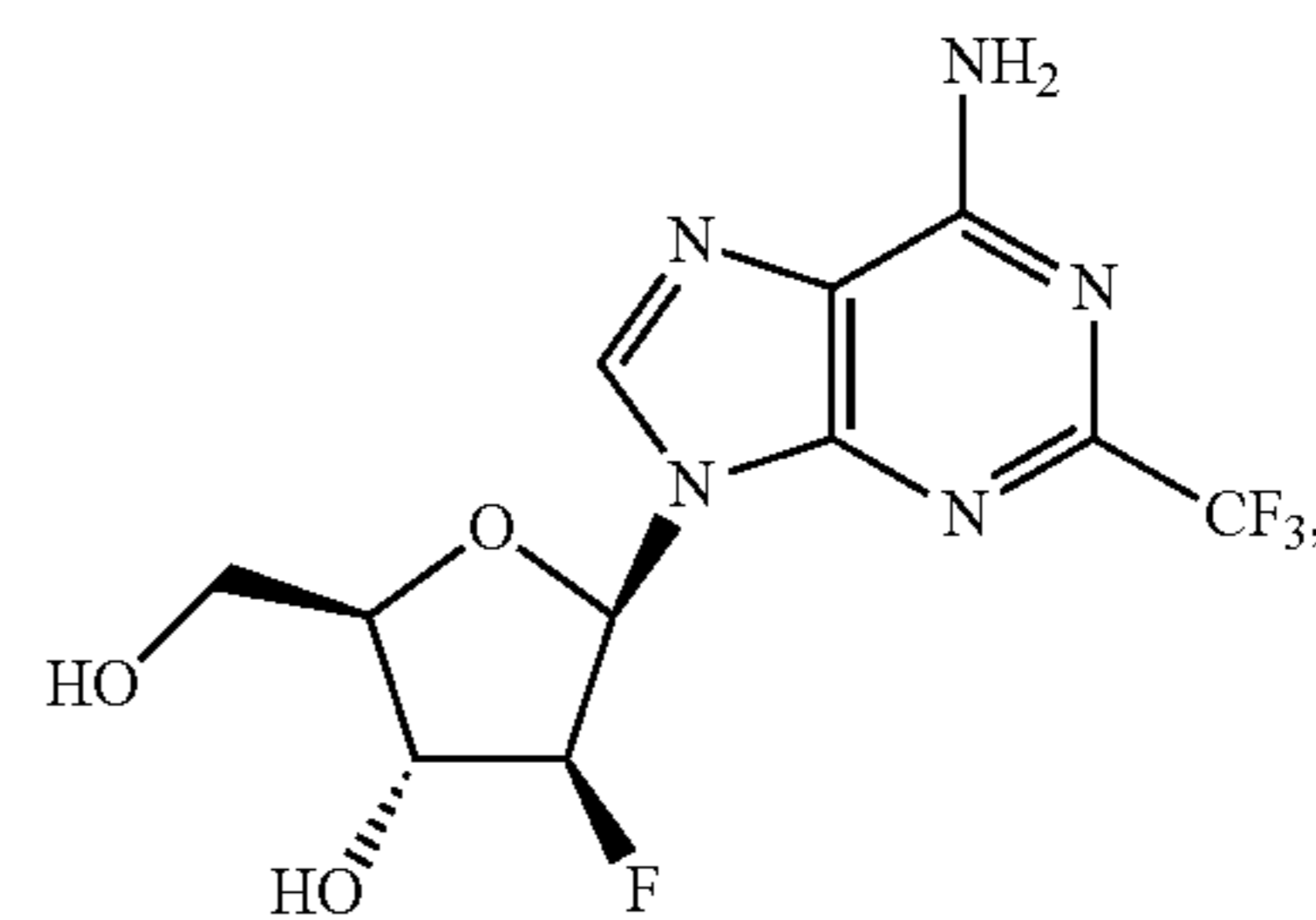
from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar¹ is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R¹ and R² together comprise a structure represented by a formula:



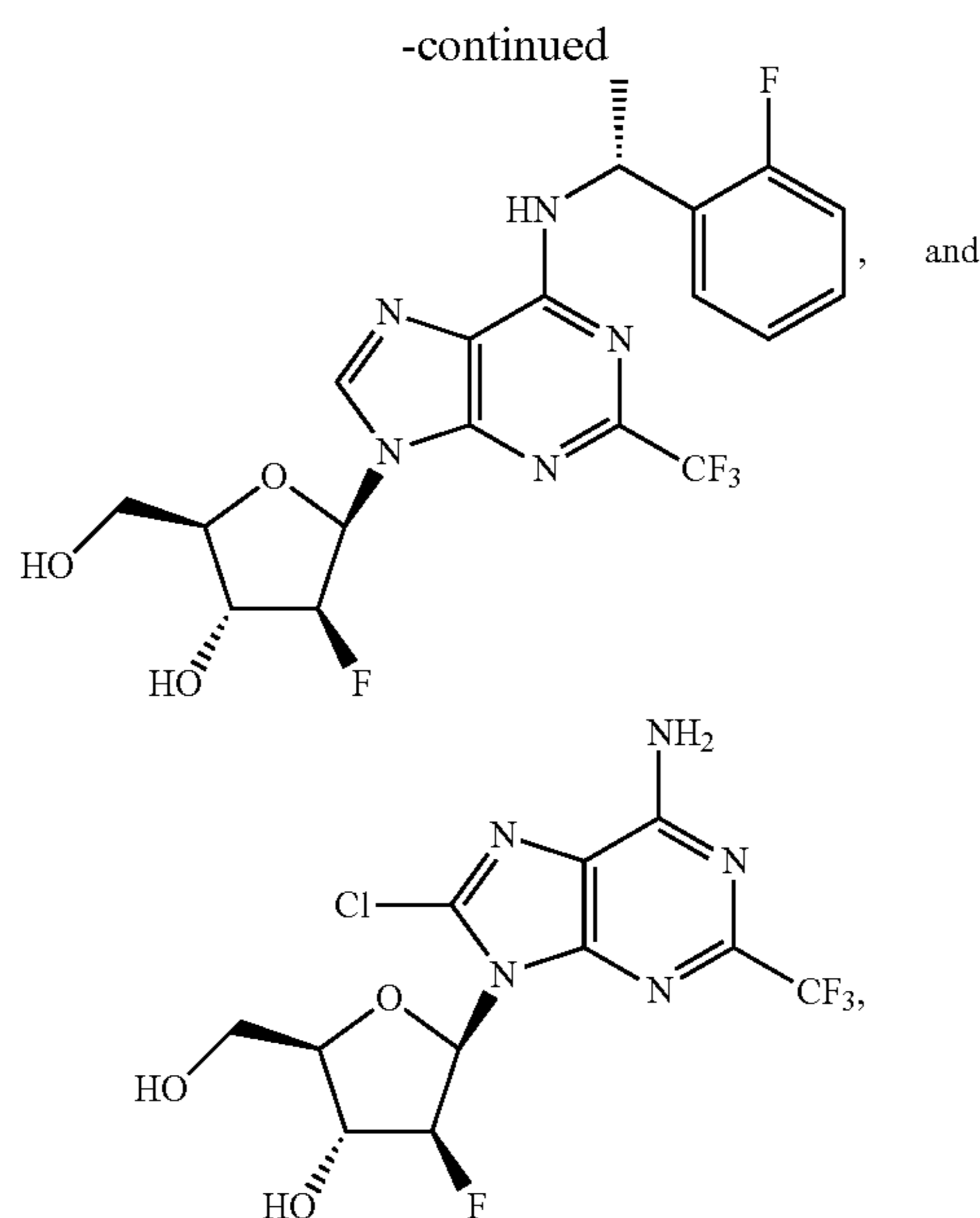
wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, C1-C12 alkyl, C1-C12 alkoxy, —C(O)R¹⁴, —(C1-C12 alkyl)CO₂H, and —(C1-C6 alkyl)Cy²; wherein R¹⁴, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH₂)R²¹; wherein R²¹, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, —(C1-C8 alkyl)NHC(NH)NH₂, —(C1-C8 alkyl)CO₂H, —(C1-C8 alkyl)C(O)NH₂, Cy³, and —(C1-C8 alkyl)Cy³; wherein Cy³, when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy², when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R⁴ is hydrogen or chlorine, provided that when each of R¹, R², R^{3a}, and R^{3b} are not simultaneously hydrogen, and provided that when each of R¹, R², and R^{3a} is hydrogen then R^{3b} is not —CH₂(unsubstituted cyclohexyl), or a pharmaceutically acceptable salt thereof, thereby modifying nucleic acid synthesis in the cell.

In one aspect, disclosed are methods of modifying nucleic acid synthesis in a cell, the method comprising contacting the cell with an effective amount of a compound having a structure selected from:

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or a pharmaceutically acceptable salt thereof, thereby modifying nucleic acid synthesis in the cell.

In various aspects, modifying is inhibiting. In a further aspect, modifying is decreasing.

In various aspects, the cell is human. In a further aspect, the cell has been isolated from a human prior to the administering step.

In various aspects, contacting is via administration to a subject. In a further aspect, the subject has been diagnosed with a need for modification of nucleic acid synthesis prior to the administering step. In a still further aspect, the subject has been diagnosed with a need for treatment of cancer prior to the administering step.

H. Additional Methods of Using the Compounds

The compounds and pharmaceutical compositions of the invention are useful in treating or controlling disorders associated with uncontrolled cellular proliferation and in particular, cancer.

Examples of disorders of uncontrolled cellular proliferation for which the compounds and compositions can be useful in treating, include, but are not limited to, cancers such as, for example, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

To treat or control the disorder, the compounds and pharmaceutical compositions comprising the compounds are administered to a subject in need thereof, such as a vertebrate, e.g., a mammal, a fish, a bird, a reptile, or an amphibian. The subject can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. The subject is preferably a mammal, such as a human. Prior to administering the compounds or compositions, the subject

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can be diagnosed with a need for treatment of a disorder of uncontrolled cellular proliferation, such as cancer.

The compounds or compositions can be administered to the subject according to any method. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. A preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. A preparation can also be administered prophylactically; that is, administered for prevention of a disorder of uncontrolled cellular proliferation, such as cancer.

The therapeutically effective amount or dosage of the compound can vary within wide limits. Such a dosage is adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg or more, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, as a continuous infusion. Single dose compositions can contain such amounts or submultiples thereof of the compound or composition to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days.

1. Use of Compounds

In one aspect, the invention relates to the use of a disclosed compound or a product of a disclosed method. In a further aspect, a use relates to the manufacture of a medicament for the treatment of a disorder of uncontrolled cellular proliferation in a subject.

Also provided are the uses of the disclosed compounds and products. In one aspect, the invention relates to use of at least one disclosed compound; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof. In a further aspect, the compound used is a product of a disclosed method of making.

In a further aspect, the use relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, for use as a medicament.

In a further aspect, the use relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of the compound or the product of a disclosed method of making.

In various aspects, the use relates to a treatment of a disorder of uncontrolled cellular proliferation in a subject. In

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one aspect, the use is characterized in that the subject is a human. In one aspect, the use is characterized in that the disorder of uncontrolled cellular proliferation is a cancer.

In a further aspect, the use relates to the manufacture of a medicament for the treatment of a disorder of uncontrolled cellular proliferation in a subject.

It is understood that the disclosed uses can be employed in connection with the disclosed compounds, products of disclosed methods of making, methods, compositions, and kits. In a further aspect, the invention relates to the use of a disclosed compound or a disclosed product in the manufacture of a medicament for the treatment of a disorder of uncontrolled cellular proliferation in a mammal. In a further aspect, the disorder of uncontrolled cellular proliferation is a cancer.

2. Manufacture of a Medicament

In one aspect, the invention relates to a method for the manufacture of a medicament for treating a disorder of uncontrolled cellular proliferation in a subject having the disorder, the method comprising combining a therapeutically effective amount of a disclosed compound or product of a disclosed method with a pharmaceutically acceptable carrier or diluent.

As regards these applications, the present method includes the administration to an animal, particularly a mammal, and more particularly a human, of a therapeutically effective amount of the compound effective in the treatment of a disorder of uncontrolled cellular proliferation. The dose administered to an animal, particularly a human, in the context of the present invention should be sufficient to affect a therapeutic response in the animal over a reasonable time-frame. One skilled in the art will recognize that dosage will depend upon a variety of factors including the condition of the animal and the body weight of the animal.

The total amount of the compound of the present disclosure administered in a typical treatment is preferably between about 0.05 mg/kg and about 100 mg/kg of body weight for mice, and more preferably between 0.05 mg/kg and about 50 mg/kg of body weight for mice, and between about 100 mg/kg and about 500 mg/kg of body weight, and more preferably between 200 mg/kg and about 400 mg/kg of body weight for humans per daily dose. This total amount is typically, but not necessarily, administered as a series of smaller doses over a period of about one time per day to about three times per day for about 24 months, and preferably over a period of twice per day for about 12 months.

The size of the dose also will be determined by the route, timing and frequency of administration as well as the existence, nature and extent of any adverse side effects that might accompany the administration of the compound and the desired physiological effect. It will be appreciated by one of skill in the art that various conditions or disease states, in particular chronic conditions or disease states, may require prolonged treatment involving multiple administrations.

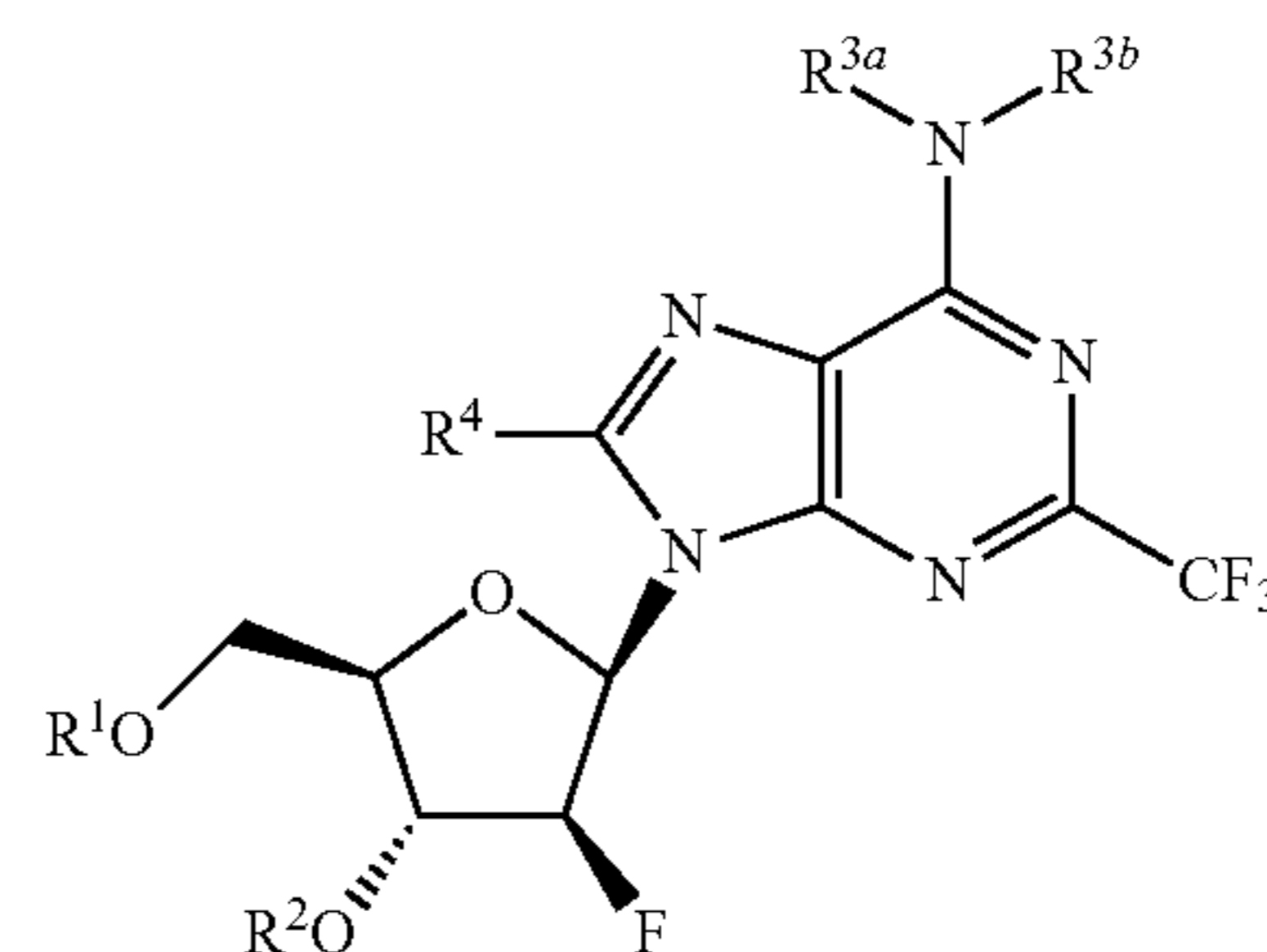
Thus, in one aspect, the invention relates to the manufacture of a medicament comprising combining a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, with a pharmaceutically acceptable carrier or diluent.

3. Kits

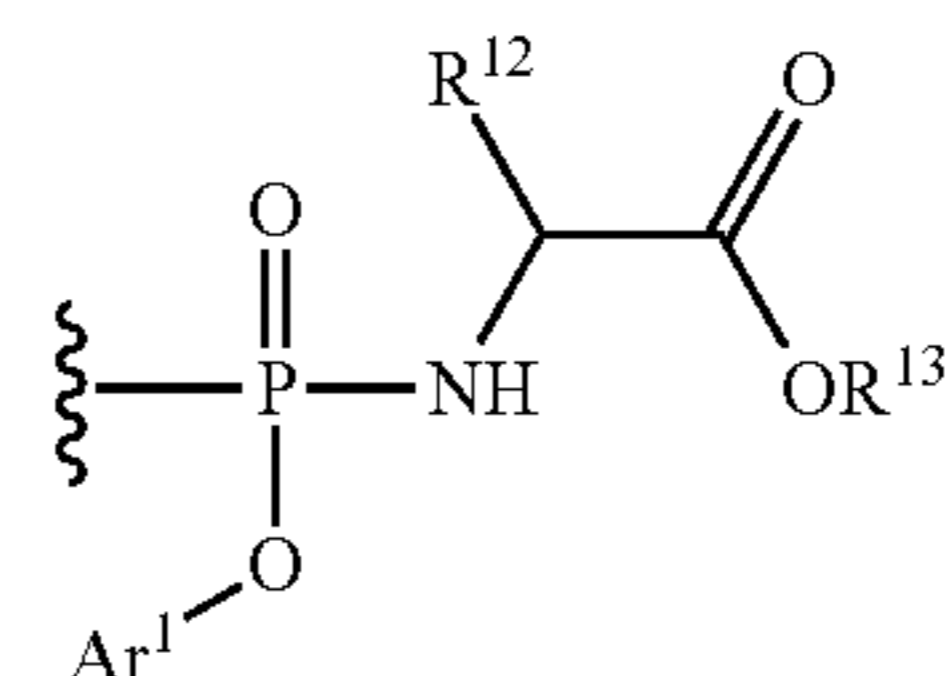
In one aspect, the invention relates to kits comprising an effective amount of a disclosed compound, and one or more of: (a) a chemotherapeutic agent; (b) instructions for administering the compound in connection with treating cancer; and (c) instructions for treating cancer.

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Thus, in one aspect, disclosed are kits comprising a compound having a structure represented by a formula:



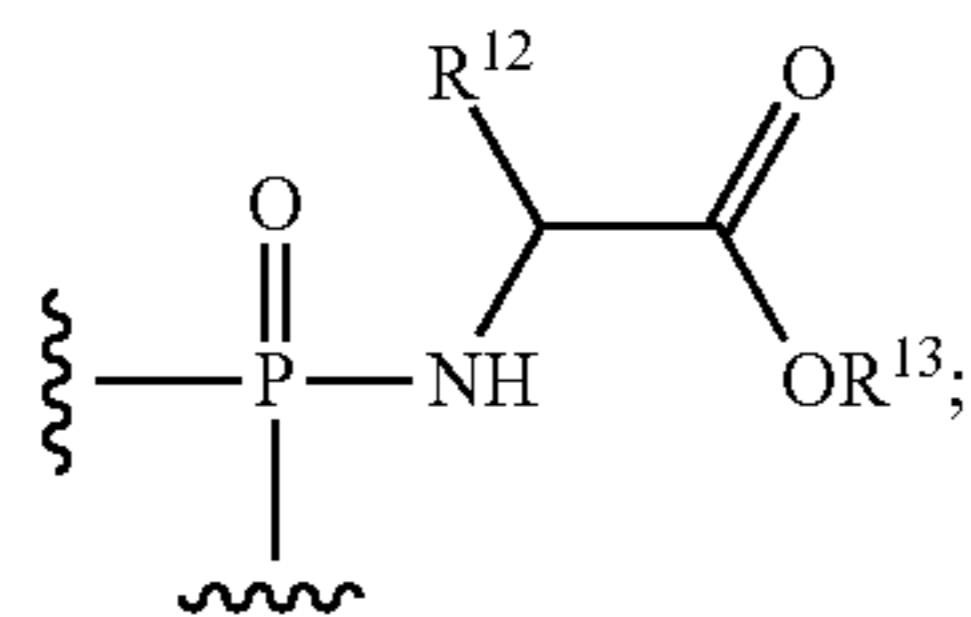
wherein one of R^1 and R^2 is hydrogen, and the other is selected from hydrogen, $-C(O)R^{10}$, $-P(O)(OR^{11})_2$, and a structure represented by a formula:



wherein R^{10} , when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and $-CH(NH_2)R^{20}$; wherein R^{20} , when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, $-(C1-C8 \text{ alkyl})NHC(NH)NH_2$, $-(C1-C8 \text{ alkyl})CO_2H$, $-(C1-C8 \text{ alkyl})C(O)NH_2$, Cy^1 , and $-(C1-C8 \text{ alkyl})Cy^1$; wherein Cy^1 , when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{11} , when present, is selected from hydrogen, C1-C30 alkyl, C1-C30 haloalkyl, $-(C1-C10 \text{ alkyl})CO_2(C1-C10 \text{ alkyl})$, $-(C1-C10 \text{ alkyl})CO_2(C1-C10 \text{ alkylthiol})$, $-(C1-C10 \text{ alkyl})-S-S-(C1-C10 \text{ alkyl})$, and Ar^2 ; wherein Ar^2 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein R^{12} , when present, is selected from hydrogen and C1-C8 alkyl; wherein R^{13} , when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3 ; wherein Ar^3 , when present, is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^1 is selected from C6-C14 aryl and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-NH_2$, $-OH$, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloal-

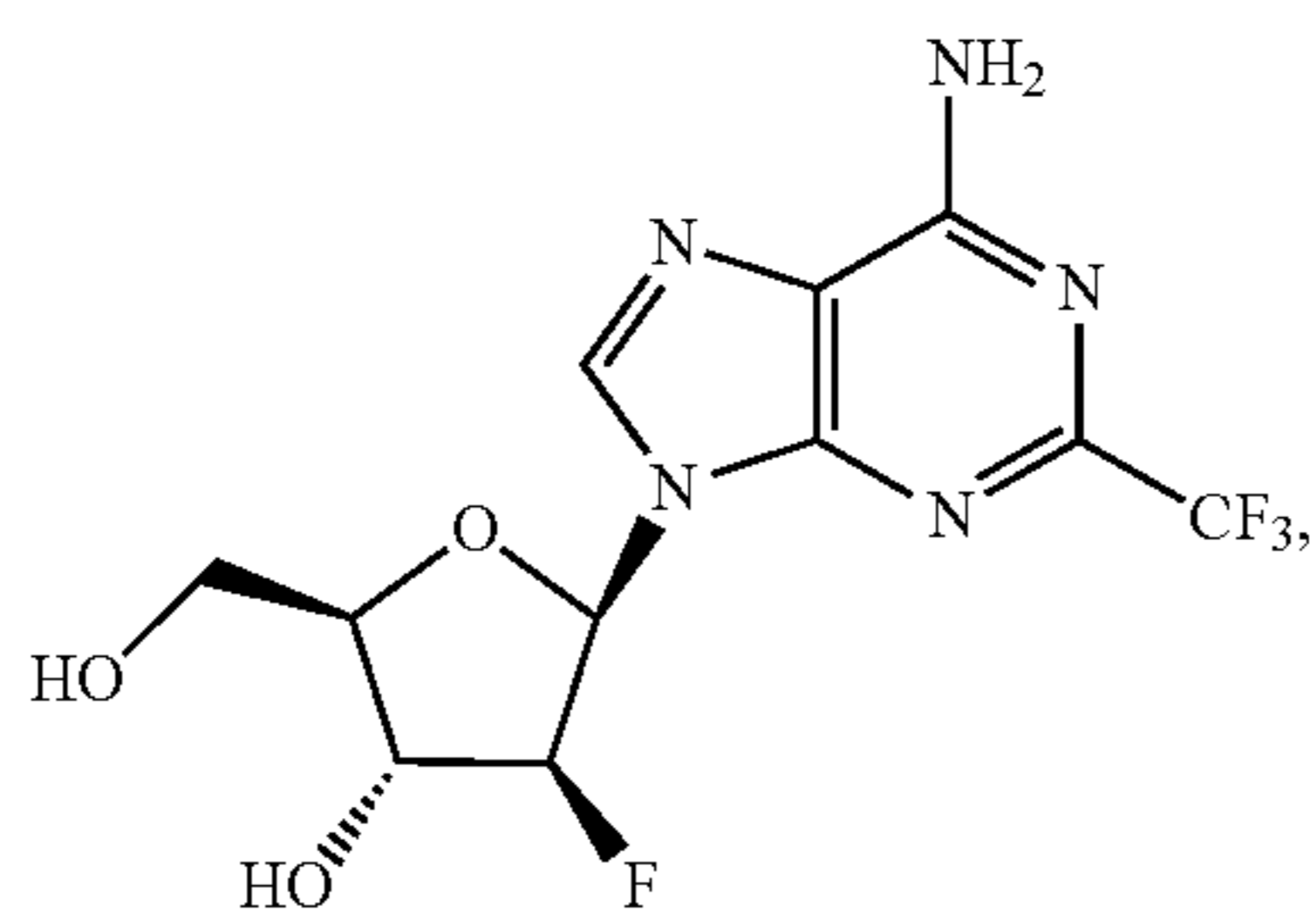
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kyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; or wherein each of R¹ and R² together comprise a structure represented by a formula:



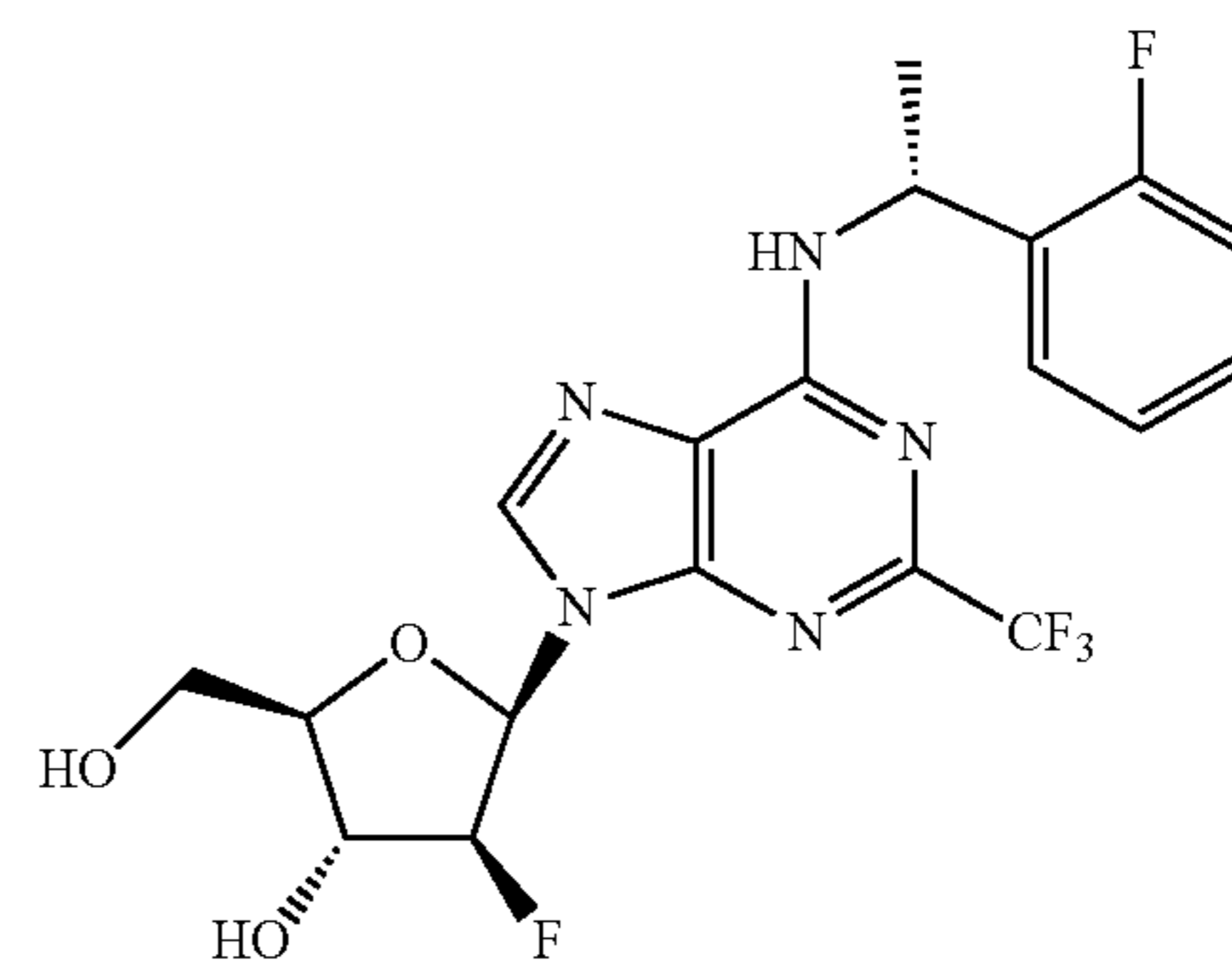
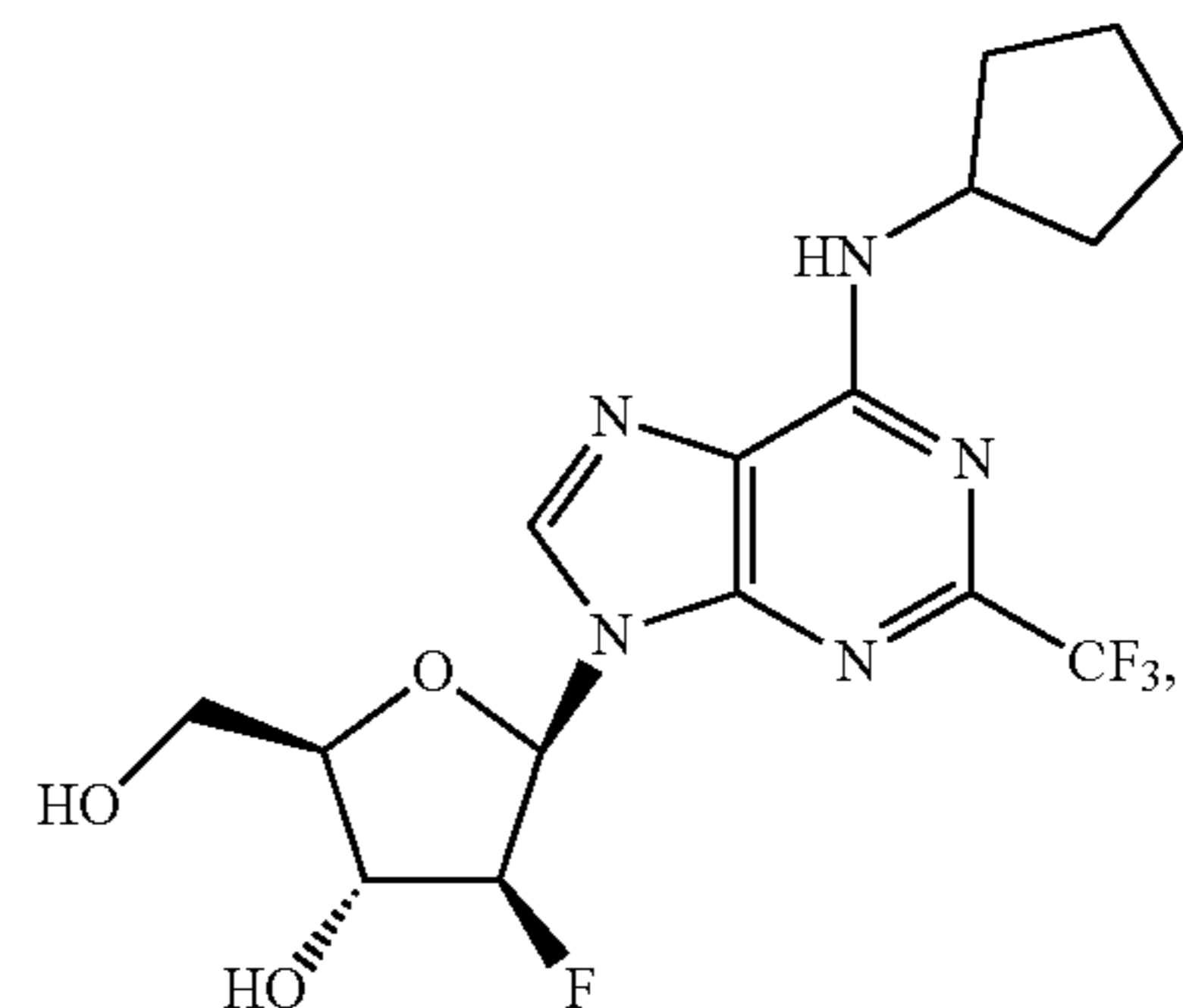
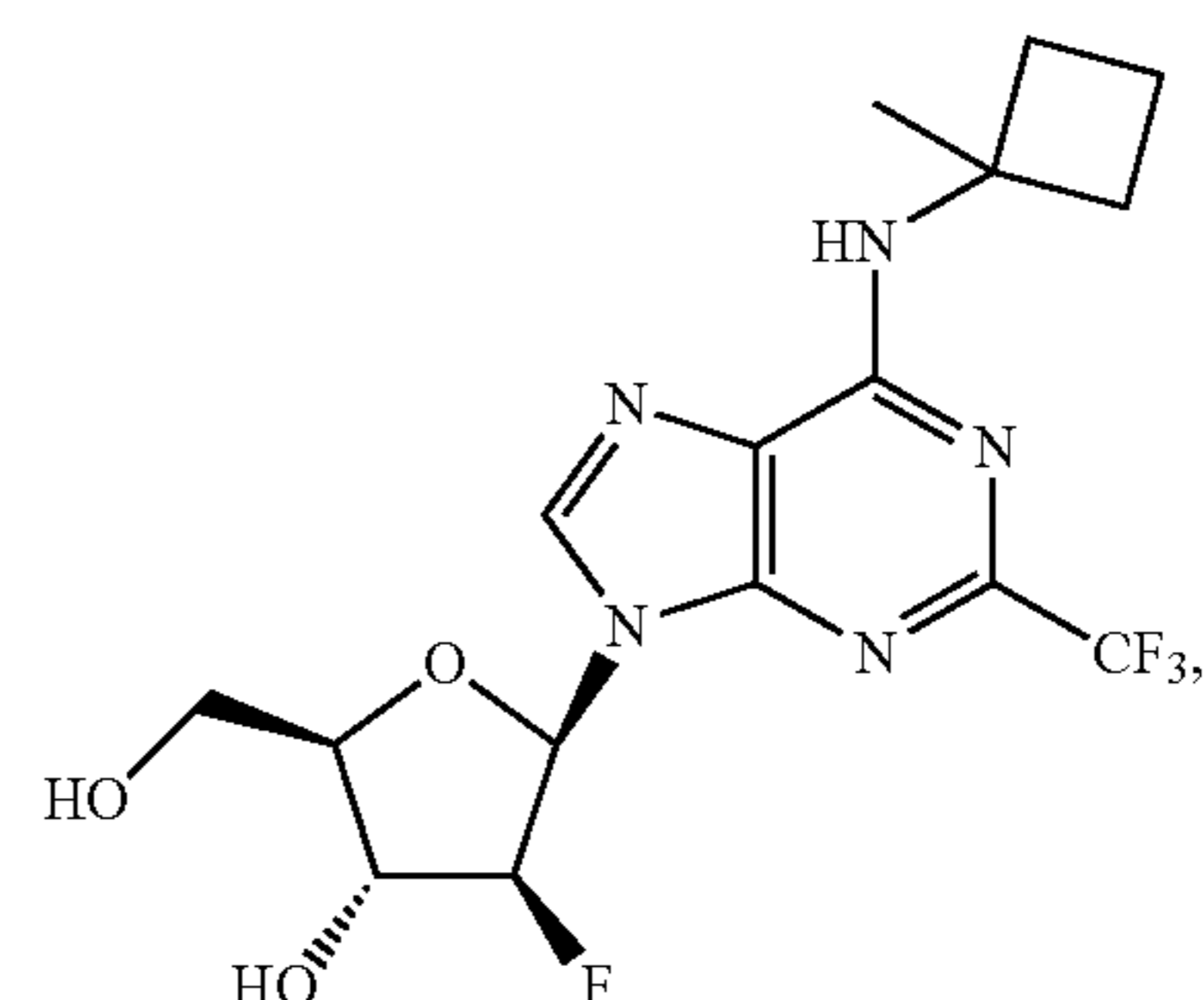
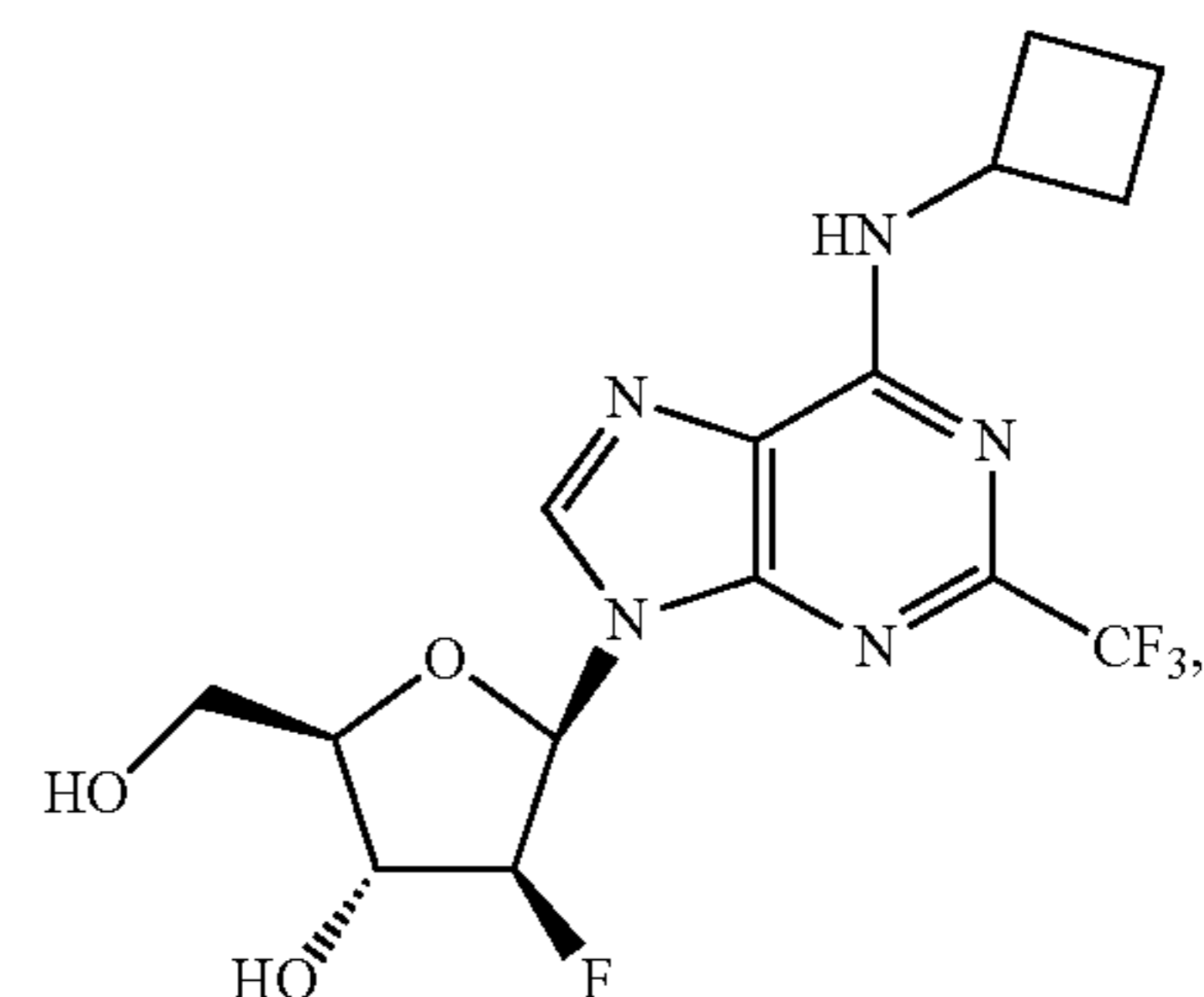
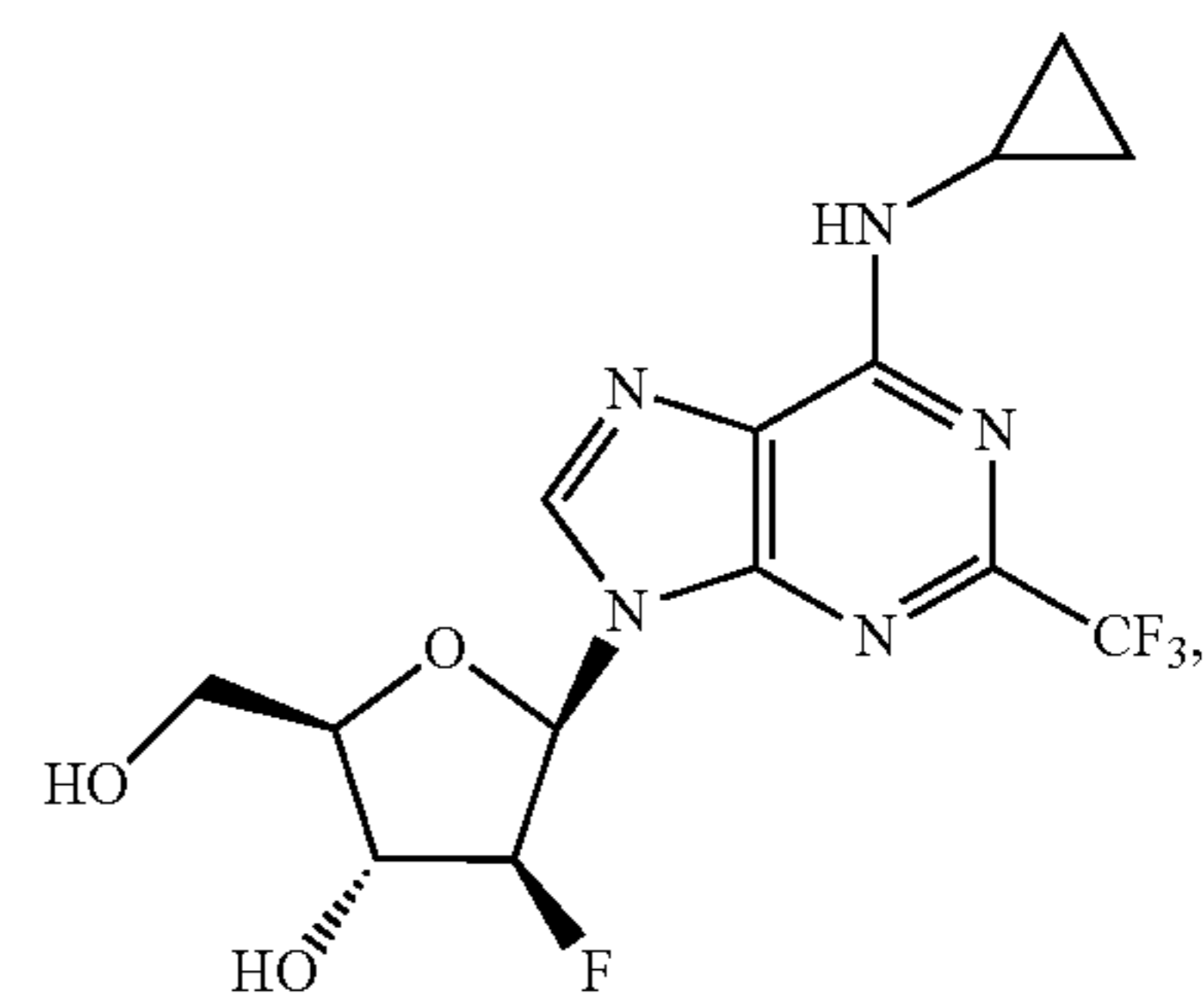
wherein each of R^{3a} and R^{3b} is independently selected from hydrogen, —OH, C1-C12 alkyl, C1-C12 alkoxy, —C(O)R¹⁴, —(C1-C12 alkyl)CO₂H, and —(C1-C6 alkyl)Cy²; wherein R¹⁴, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH₂)R²¹; wherein R²¹, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylthiol, C1-C8 aminoalkyl, C1-C8 alkylselenide, —(C1-C8 alkyl)NHC(NH)NH₂, —(C1-C8 alkyl)CO₂H, —(C1-C8 alkyl)C(O)NH₂, Cy³, and —(C1-C8 alkyl)Cy³; wherein Cy³, when present, is selected from C3-C6 cycloalkyl, C3-C6 heterocycloalkyl, C6-C14 aryl, and C2-C10 heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Cy², when present, is selected from C3-C6 cycloalkyl and C3-C6 heterocycloalkyl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —CN, —NH₂, —OH, —NO₂, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein R⁴ is hydrogen or chlorine, provided that when each of R¹, R², R^{3a}, and R^{3b} are not simultaneously hydrogen, and provided that when each of R¹, R², and R^{3a} is hydrogen then R^{3b} is not —CH₂(unsubstituted cyclohexyl), or a pharmaceutically acceptable salt thereof, and one or more of: (a) a chemotherapeutic agent; (b) instructions for administering the compound in connection with treating cancer; and (c) instructions for treating cancer.

In one aspect, disclosed are kits comprising a compound having a structure selected from:



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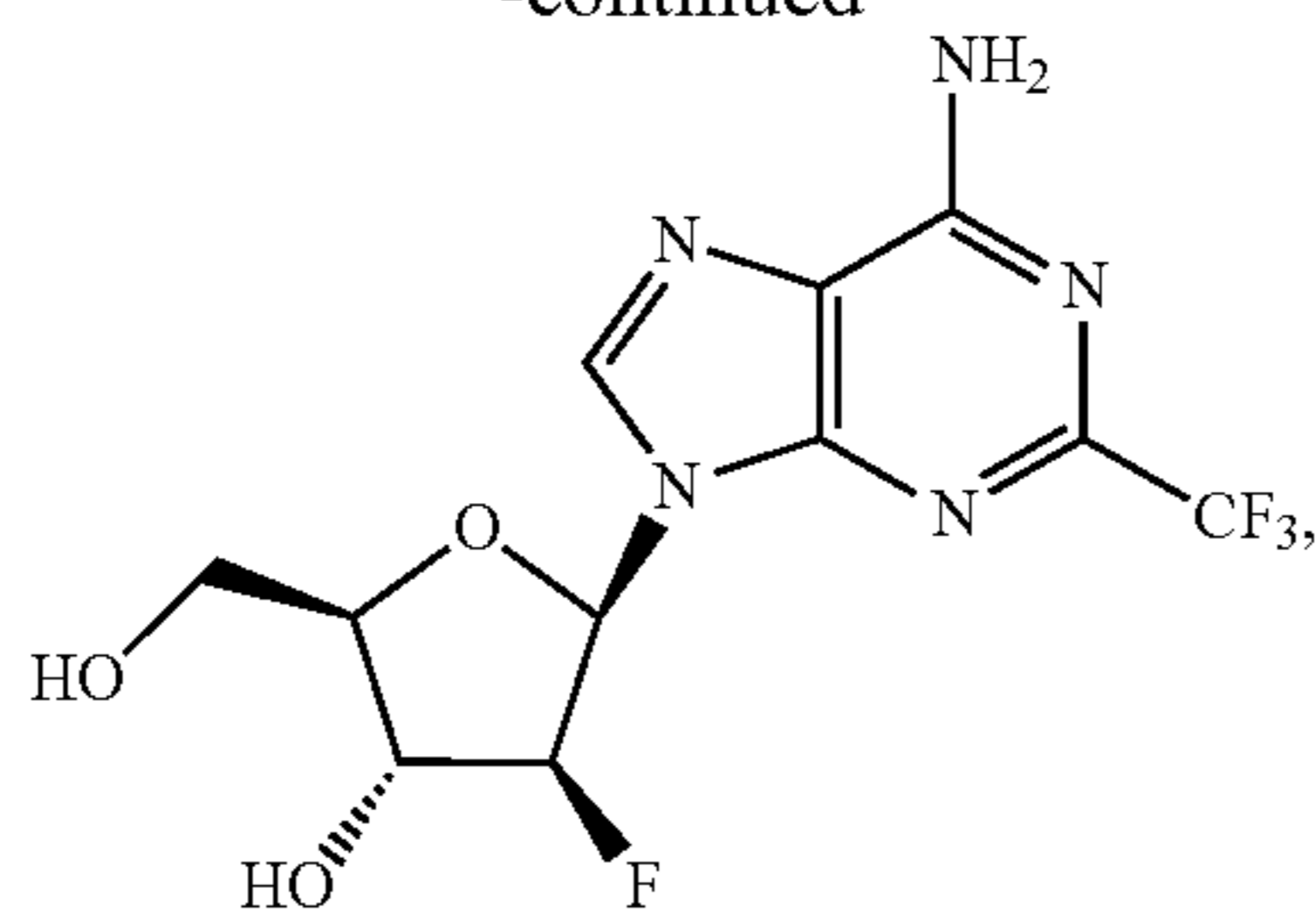
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, and

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or a pharmaceutically acceptable salt thereof, and one or more of: (a) a chemotherapeutic agent; (b) instructions for administering the compound in connection with treating cancer; and (c) instructions for treating cancer.

In a further aspect, the cancer is selected from a sarcoma, a carcinoma, a hematological cancer, a solid tumor, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanoma, glioma, leukemia, lymphoma, chronic myeloproliferative disorder, myelodysplastic syndrome, myeloproliferative neoplasm, and plasma cell neoplasm (myeloma). In yet a further aspect, the cancer is a solid tumor. In an even further aspect, the cancer is breast cancer.

In a further aspect, the chemotherapeutic agent is selected from an alkylating agent, an antimetabolite agent, an anti-neoplastic antibiotic agent, a mitotic inhibitor agent, and a mTor inhibitor agent.

In a further aspect, the antineoplastic antibiotic agent is selected from doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plinamycin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt thereof.

In a further aspect, the antimetabolite agent is selected from gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt thereof.

In a further aspect, the alkylating agent is selected from carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt thereof.

In a further aspect, the mitotic inhibitor agent is selected from irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etoposide, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt thereof.

In a further aspect, the mTor inhibitor agent is selected from everolimus, sirolimus, and temsirolimus, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

In a further aspect, the compound and the chemotherapeutic agent are co-formulated. In a further aspect, the compound and the chemotherapeutic agent are co-packaged.

The kits can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another component for delivery to a patient.

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It is understood that the disclosed kits can be prepared from the disclosed compounds, products, and pharmaceutical compositions. It is also understood that the disclosed kits can be employed in connection with the disclosed methods of using.

The foregoing description illustrates and describes the disclosure. Additionally, the disclosure shows and describes only the preferred embodiments but, as mentioned above, it is to be understood that it is capable to use in various other combinations, modifications, and environments and is capable of changes or modifications within the scope of the invention concepts as expressed herein, commensurate with the above teachings and/or the skill or knowledge of the relevant art. The embodiments described herein above are further intended to explain best modes known by applicant and to enable others skilled in the art to utilize the disclosure in such, or other, embodiments and with the various modifications required by the particular applications or uses thereof. Accordingly, the description is not intended to limit the invention to the form disclosed herein. Also, it is intended to the appended claims be construed to include alternative embodiments.

All publications and patent applications cited in this specification are herein incorporated by reference, and for any and all purposes, as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. In the event of an inconsistency between the present disclosure and any publications or patent application incorporated herein by reference, the present disclosure controls.

I. Examples

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

The Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way. Examples are provided herein to illustrate the invention and should not be construed as limiting the invention in any way.

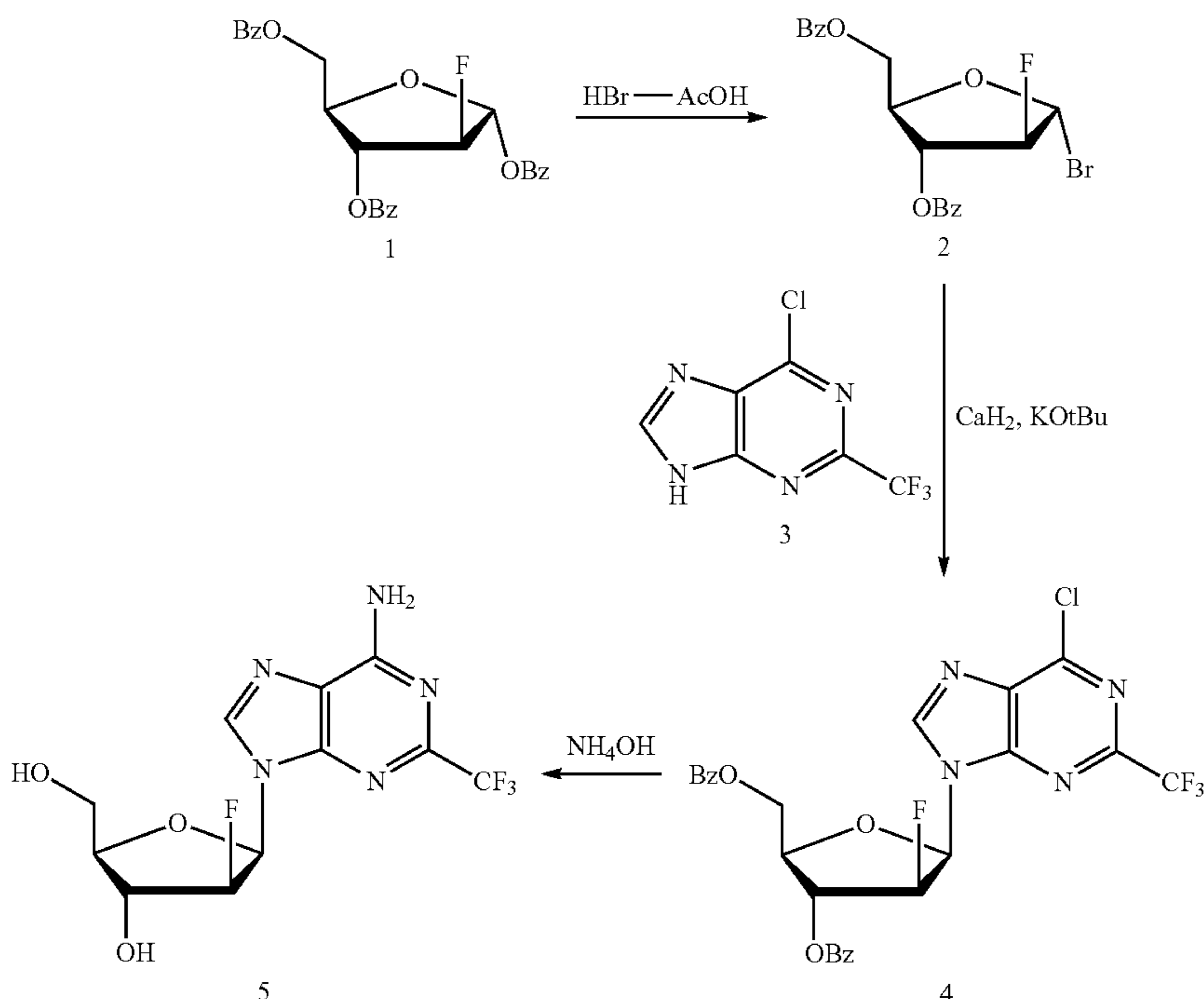
1. Chemistry Experimentals

The reactions were performed under argon atmosphere and reaction temperatures were measured externally. Anhydrous solvents were obtained from Aldrich and used as received. Microwave (MW) reactions were performed in a Biotage Initiator+ equipped with Robot Eight microwave system. The reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel (60F₂₅₄) glass plates from E. Merck and visualized using UV light (254 nm). Purification of compounds was carried out by flash chromatography using Combiflash® R_f with Teledyne Isco RediSep R_f columns. Pure samples were dried overnight under high vacuum before analyses. The high resolution electrospray ionization mass spectral data (HR-ESIMS) were obtained on an Agilent LC-MS TOF. ¹H NMR spectra were recorded at 400 MHz on Agilent/Varian MR-400 spectrometer in CDCl₃ or DMSO-d₆ as solvents. The chemi-

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cal shifts (δ) are in ppm downfield from standard tetramethylsilane (TMS), referenced to 0.00 ppm (δ). All final compounds with reported biological data had purity $\geq 95\%$, which was determined by analytical HPLC performed on an Agilent 1100 LC equipped with a diode array UV detector and monitored at 254 nm.

A. Procedure for the Synthesis of 2'-deoxy-2'-fluoroarabinosyl nucleoside (5)



(i) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-5-bromo-4-fluoro-tetrahydrofuran-2-yl]methyl benzoate (2)

To a cold (-5°C .) solution of (2R,3S,4R,5R)-5-((benzyloxy)methyl)-3-fluoro-2,4-dihydroxy-2H-tetrahydrofuran-3-yl methyl benzoate 1 (3.0 g, 6.46 mmol, 1.0 eq) in anhydrous dichloromethane (15 mL) was added 33% hydrobromic acid (3.5 mL, 19.4 mmol, 3.0 eq) in acetic acid, dropwise, over 20 minutes. Upon completion of addition, the reaction mixture was stirred for 18 hrs as it warmed to 20°C . The reaction mixture was evaporated under reduced pressure to give a red oil, which was dissolved in dichloromethane (100 mL) and then washed with water (3 \times 50 mL), saturated aqueous NaHCO_3 (2 \times 50 mL) and brine (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 , filtered, and then the filtrate was evaporated under reduced pressure. The oil obtained was further dried under vacuum (2 hrs) to provide 2.67 g (98%) of 2 as a brown oil. ^1H NMR (400 MHz, CDCl_3) δ 8.14-8.02 (m, 4H), 7.66-7.38 (m, 6H), 6.64 (dt, $J=12.1, 0.9$ Hz, 1H), 5.67-5.49 (m, 2H), 4.86-4.67 (m, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -165.81 to -166.11 (m, 1F).

(ii) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-5-[6-chloro-2-(trifluoromethyl)purin-9-yl]-4-fluoro-tetrahydrofuran-2-yl]methyl benzoate (4)

To a suspension of the nucleobase 3 (1.0 g, 4.49 mmol, 1.0 eq), potassium tert-butoxide (529 mg, 4.72 mmol, 1.05 eq),

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and calcium hydride (189 mg, 4.49 mmol) in anhydrous acetonitrile (10 mL) was added a solution of the brominated sugar 2 (2.28 g, 5.39 mmol, 1.2 eq) in anhydrous 1,2-dichloroethane (10 mL). The resulting mixture was stirred at 50°C . for 16 hrs. The reaction mixture was filtered through celite and eluted with ethyl acetate. The filtrate was evaporated under reduced pressure to give a crude product. Purification by flash chromatography (40 g gold silica column, 0-50% ethyl acetate in hexanes, gradient elution) provided an oil, which upon trituration in hexanes and

filtration provided 1.74 g (69%) of 4 as a white powder. ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, $J=3.0$ Hz, 1H), 8.18-8.05 (m, 4H), 7.74-7.42 (m, 6H), 6.74 (dd, $J=21.4, 2.9$ Hz, 1H), 5.81 (dd, $J=17.2, 2.9$ Hz, 1H), 5.55-5.33 (m, 1H), 4.91-4.79 (m, 2H), 4.65 (q, $J=4.1$ Hz, 1H); ^{19}F NMR (376 MHz, CDCl_3) δ -68.59 (s, 3F), -197.02 to -197.32 (m, 1F); LCMS m/z 565.0 (M+H) $^+$.

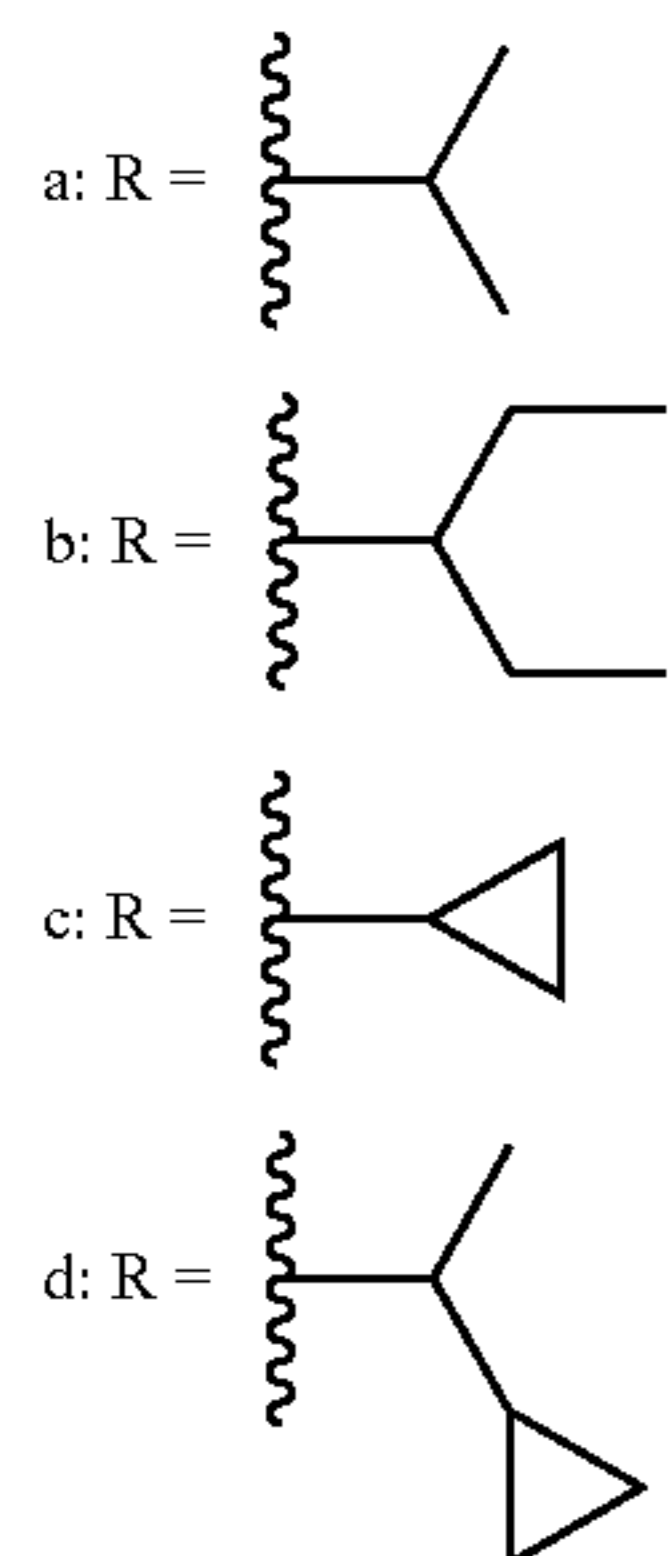
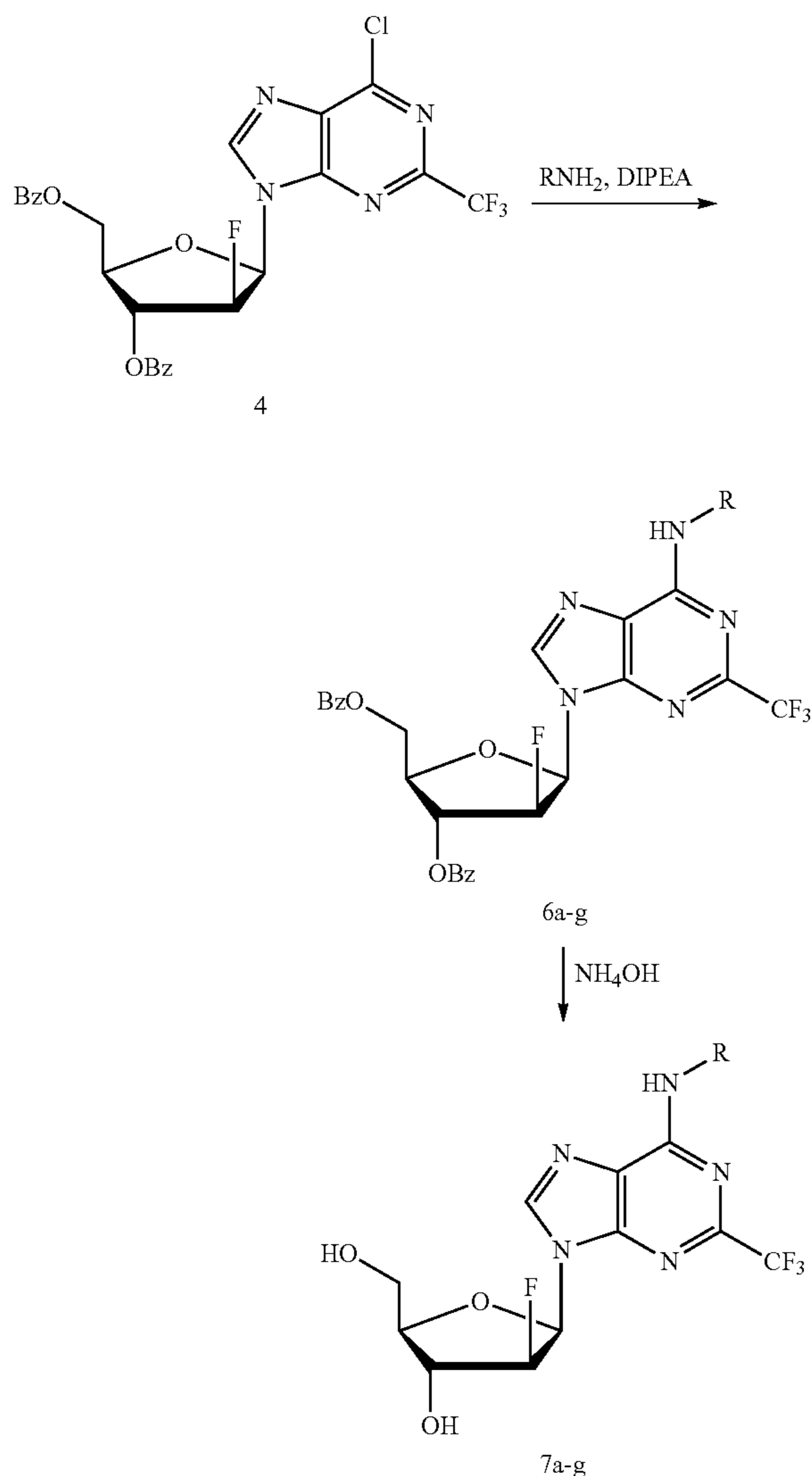
(iii) Preparation of (2R,3R,4S,5R)-5-[6-amino-2-(trifluoromethyl)purin-9-yl]-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (5)

To a heavy wall glass pressure vessel was added the nucleoside 4 (1.0 g, 1.77 mmol, 1.0 eq), 1,4-dioxane (10 mL), followed by 28% aqueous ammonium hydroxide (49 mL, 354.1 mmol, 200.0 eq). The resulting mixture was stirred at 80°C . for 72 hrs. The reaction mixture was evaporated under reduced pressure to afford a crude product, which was purified by flash chromatography (24 g silica column, 0-10% methanol in dichloromethane, gradient elution) to provide 505 mg (83%) of 5 as a white powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.46 (d, $J=2.0$ Hz, 1H), 8.01 (s, 2H), 6.43 (dd, $J=13.6, 4.7$ Hz, 1H), 5.99 (d, $J=5.1$ Hz, 1H), 5.28 (dt, $J=52.6, 4.4$ Hz, 1H), 5.07 (t, $J=5.7$ Hz, 1H), 4.56-4.39 (m, 1H), 3.87 (q, $J=5.0$ Hz, 1H), 3.67 (qd, $J=12.1, 6.6$ Hz, 2H); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -68.02 (s,

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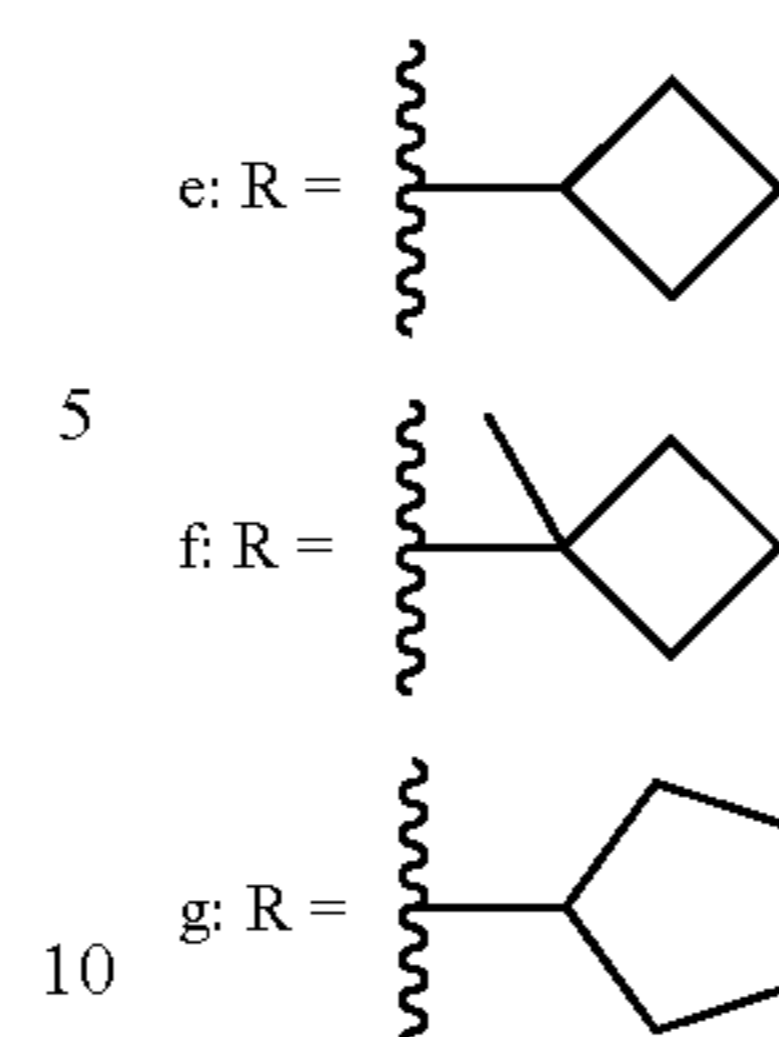
3F), -198.08 (m, 1F); LCMS m/z 338.0 (M+H)⁺; HRMS calc for C₁₁H₁₁F₄N₅O₃·H, 338.08708, found, 338.08742; HPLC 97.9% at 254 nm.

b. Procedure for the Synthesis of
2'-deoxy-2'-fluoroarabinosyl nucleoside analogs
(7a-g)

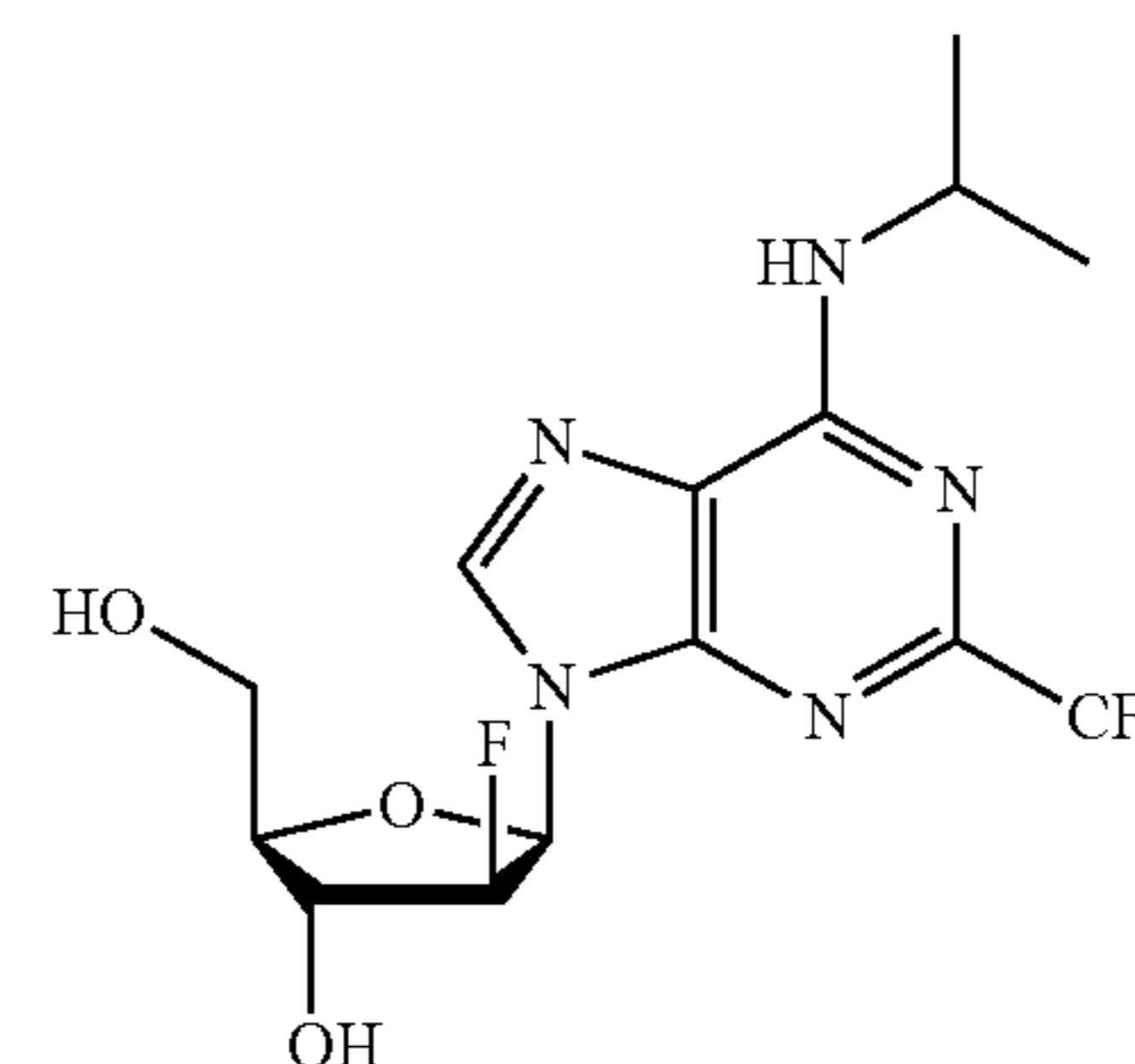


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(i) Synthesis of (2R,3R,4S,5R)-4-fluoro-2-(hydroxymethyl)-5-(6-(isopropylamino)-2-(trifluoromethyl)purin-9-yl)tetrahydrofuran-3-ol (7a)



1) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-4-fluoro-5-[6-(isopropylamino)-2-(trifluoromethyl)purin-9-yl]tetrahydrofuran-2-yl]methyl benzoate (6a)

A solution of the nucleoside 4 (100 mg, 0.18 mmol, 1.0 eq), isopropylamine (0.023 mL, 0.27 mmol, 1.5 eq) and N,N-diisopropylethylamine (0.062 mL, 0.35 mmol, 2.0 eq) in anhydrous 1,4-dioxane (3 mL) was stirred at 80° C. for 18 hrs under argon. The reaction mixture was evaporated under reduced pressure and the crude product was purified by flash chromatography (12 g gold silica column, 0-50% ethyl acetate in hexanes, gradient elution) to provide 102 mg (98%) of 6a as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.15-8.06 (m, 5H), 7.71-7.39 (m, 6H), 6.64 (dd, J=22.3, 2.9 Hz, 1H), 5.78 (dd, J=17.5, 3.1 Hz, 2H), 5.38 (dd, J=49.9, 2.9 Hz, 1H), 4.85-4.76 (m, 2H), 4.57 (q, J=4.2 Hz, 2H), 1.33 (d, J=6.5 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -69.69 (s, 3F), -197.26 to -197.62 (m, 1F); LCMS m/z 587.7 (M+H)⁺.

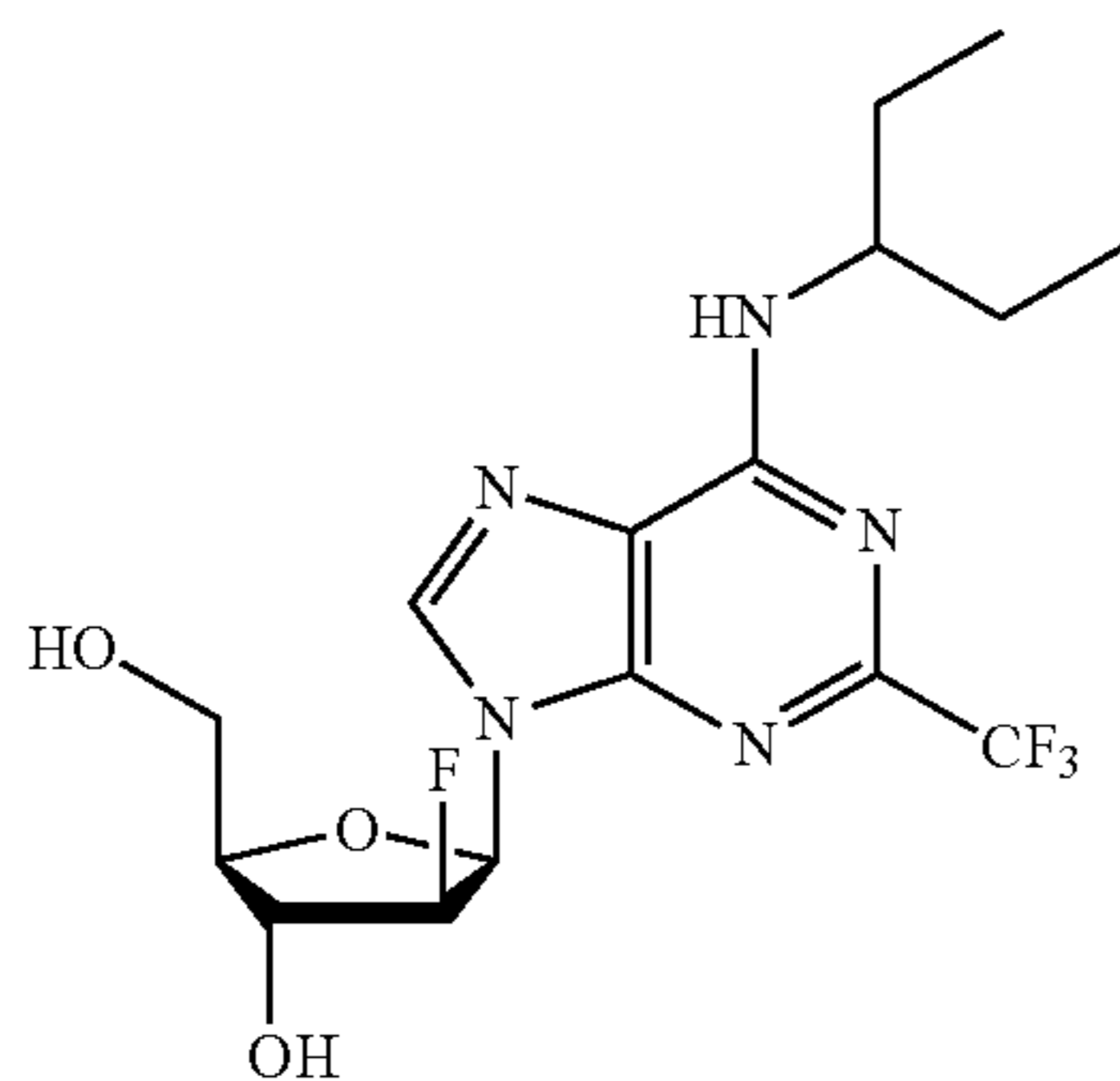
2) Preparation of 7a

A mixture of the nucleoside 6a (95 mg, 0.16 mmol, 1.0 eq) and potassium carbonate (67 mg, 0.49 mmol, 3.0 eq) in methanol (5 mL) was stirred at room temperature for 18 hrs. The reaction mixture was neutralized to pH 6-7 using glacial acetic acid (3 drops) and the solvent was removed under reduced pressure to give a crude product, which was purified by flash chromatography (12 g gold silica column, 0-10% methanol in dichloromethane, gradient elution) to provide 48 mg (77%) of 7a as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.45 (d, J=2.0 Hz, 1H), 8.34 (d, J=8.4 Hz, 1H), 6.43 (dd, J=13.6, 4.7 Hz, 1H), 5.98 (d, J=5.0 Hz, 1H), 5.27 (dt, J=52.6, 4.3 Hz, 1H), 5.06 (t, J=5.7 Hz, 1H), 4.47 (dp,

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J=19.7, 5.1 Hz, 2H), 3.91-3.83 (m, 1H), 3.67 (tq, J=11.8, 6.3, 5.6 Hz, 2H), 1.24 (d, J=6.5 Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -68.23 (s, 3F), -198.15 (m, 1F); LCMS m/z 379.9 (M+H) $^+$; HRMS calc for $\text{C}_{14}\text{H}_{17}\text{F}_4\text{N}_5\text{O}_3\cdot\text{H}$, 380.13403, found, 380.13405; HPLC 99.7% at 254 nm.

(ii) Synthesis of (2R,3R,4S,5R)-5-[6-(1-ethylpropylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (7b)



1) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-5-[6-(1-ethylpropylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-tetrahydrofuran-2-yl]methyl benzoate (6b)

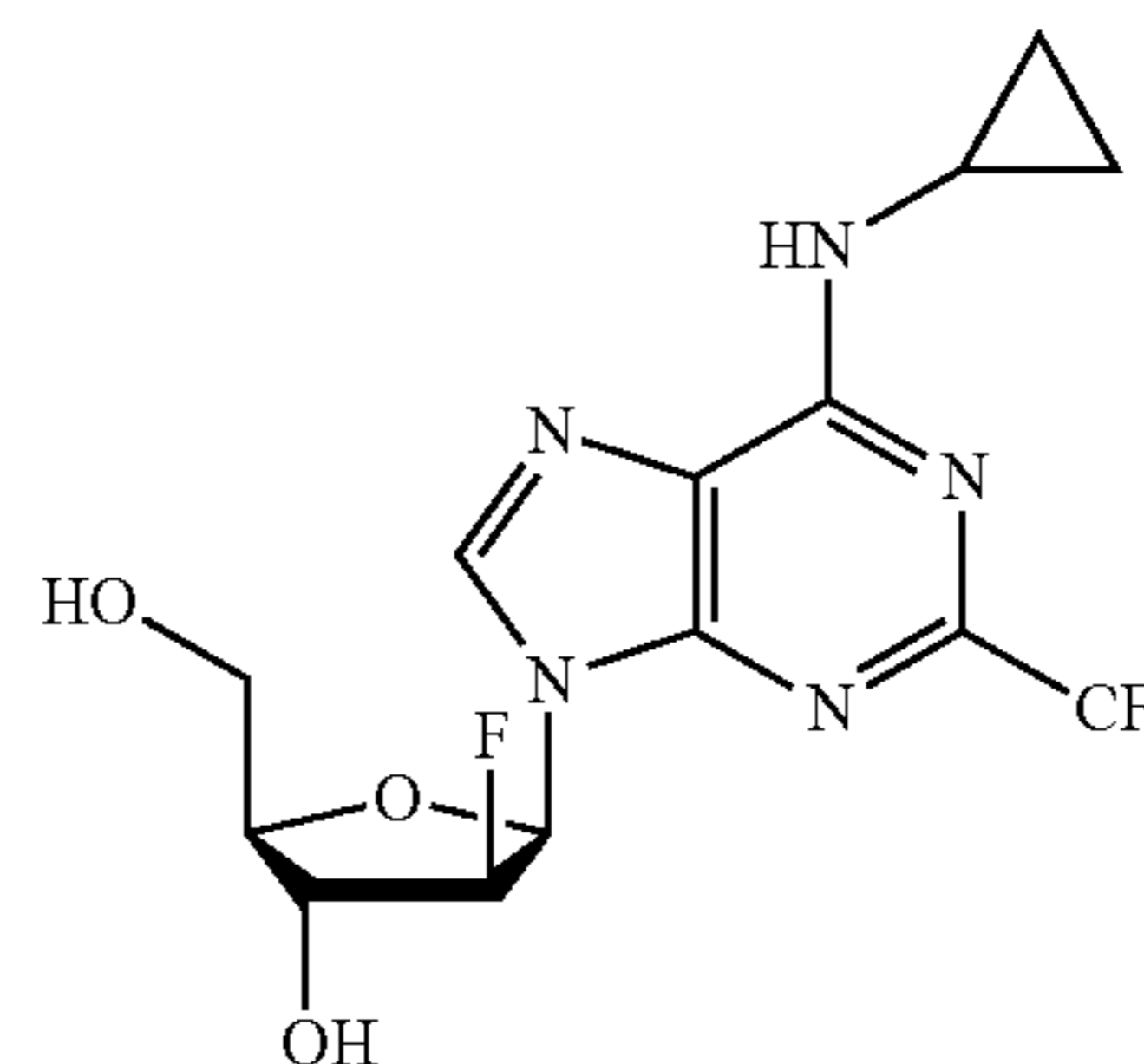
Intermediate 6b was prepared from 4 (100 mg, 0.18 mmol, 1.0 eq) and 3-aminopentane (0.031 mL, 0.27 mmol, 1.5 eq) in anhydrous 1,4-dioxane (3 mL) with N,N-diisopropylethylamine (0.062 mL, 0.35 mmol, 2.0 eq) as base according to the procedure described for the preparation of 6a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-50% ethyl acetate in hexanes, gradient elution) provided 107 mg (98%) of 6b as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.22-8.07 (m, 5H), 7.72-7.41 (m, 6H), 6.64 (dd, J=22.3, 2.9 Hz, 1H), 5.85-5.71 (m, 2H), 5.38 (dd, J=49.7, 2.9 Hz, 1H), 4.91-4.75 (m, 2H), 4.57 (q, J=4.2 Hz, 1H), 4.31 (s, 1H), 1.73 (ddd, J=13.4, 7.5, 5.6 Hz, 2H), 1.56 (dp, J=14.7, 7.5 Hz, 2H), 0.95 (td, J=7.4, 2.7 Hz, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -69.71 (s, 3F), -197.23 to -197.56 (m, 1F); LCMS m/z 615.8 (M+H) $^+$.

2) Preparation of 7b

The final target 7b was prepared from 6b (98 mg, 0.16 mmol, 1.0 eq) and potassium carbonate (66 mg, 0.48 mmol, 3.0 eq) in methanol (5 mL) according to the procedure described for the preparation of 7a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-10% methanol in dichloromethane, gradient elution) provided 21 mg (33%) of 7b as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.44 (t, J=2.8 Hz, 1H), 8.23 (d, J=8.6 Hz, 1H), 6.43 (dd, J=13.7, 4.7 Hz, 1H), 6.01-5.95 (m, 1H), 5.27 (dt, J=52.5, 4.3 Hz, 1H), 5.06 (t, J=5.7 Hz, 1H), 4.48 (dd, J=18.9, 4.8 Hz, 1H), 4.14 (h, J=7.6 Hz, 1H), 3.87 (q, J=5.0 Hz, 1H), 3.75-3.58 (m, 2H), 1.59 (ddt, J=20.9, 14.7, 7.3 Hz, 4H), 0.93-0.80 (m, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -68.32 (s, 3F), -197.99 (m, 1F); LCMS m/z 407.9 (M+H) $^+$; HRMS calc for $\text{C}_{16}\text{H}_{21}\text{F}_4\text{N}_5\text{O}_3\cdot\text{H}$, 408.16533, found, 408.16507; HPLC 99.5% at 254 nm.

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(iii) Synthesis of (2R,3R,4S,5R)-5-[6-(cyclopropylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (7c)



1) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-5-[6-(cyclopropylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-tetrahydrofuran-2-yl]methyl benzoate (6c)

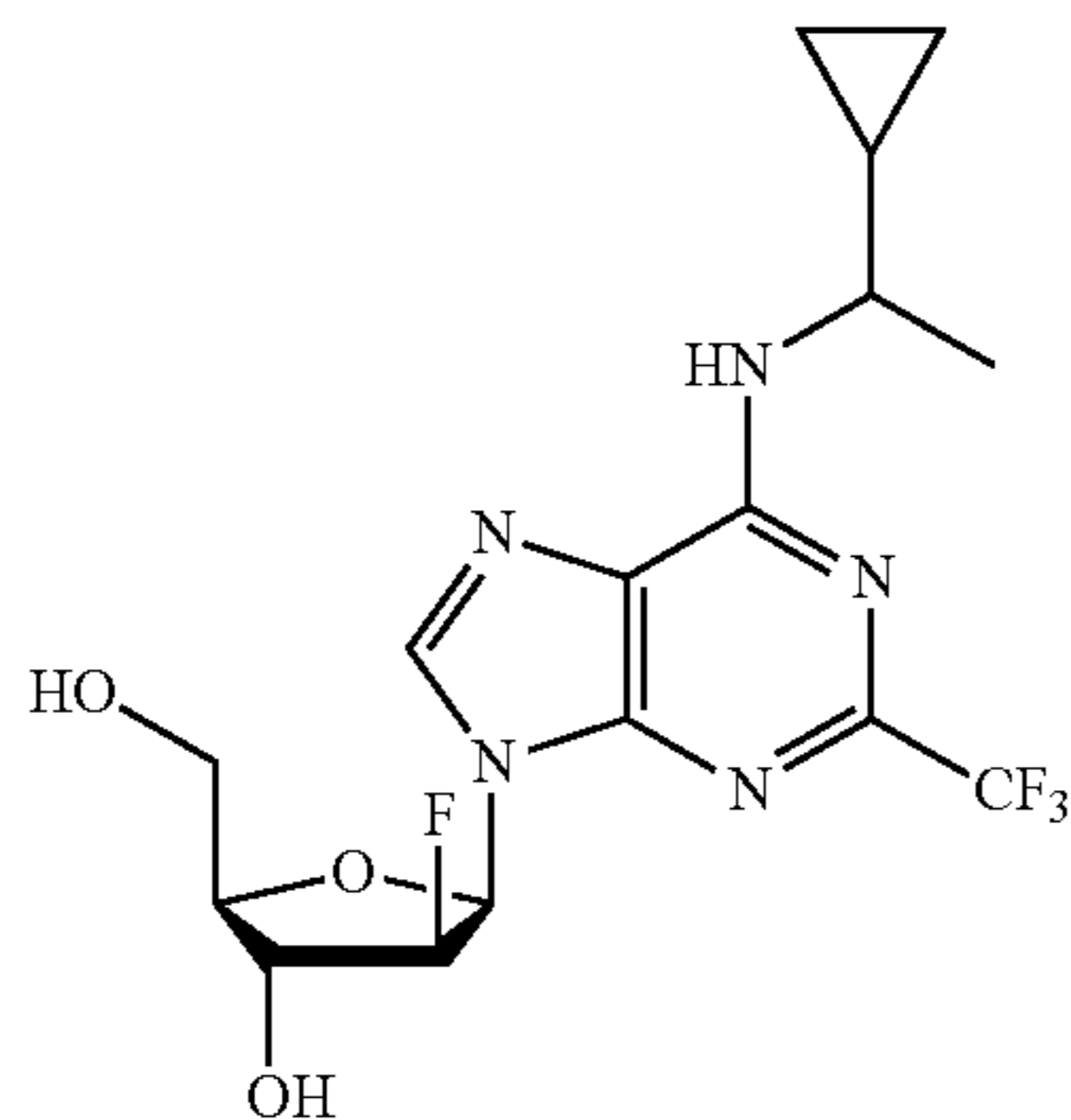
Intermediate 6c was prepared from 4 (100 mg, 0.18 mmol, 1.0 eq) and cyclopropylamine (0.018 mL, 0.27 mmol, 1.5 eq) in anhydrous 1,4-dioxane (3 mL) with N,N-diisopropylethylamine (0.062 mL, 0.35 mmol, 2.0 eq) as base according to the procedure described for the preparation of 6a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-50% ethyl acetate in hexanes, gradient elution) provided 93 mg (90%) of 6c as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.17-8.07 (m, 5H), 7.70-7.63 (m, 1H), 7.61-7.50 (m, 3H), 7.45 (t, J=7.8 Hz, 2H), 6.65 (dd, J=22.3, 2.9 Hz, 1H), 6.09 (s, 1H), 5.79 (dd, J=17.5, 3.0 Hz, 1H), 5.38 (dd, J=50.1, 2.9 Hz, 1H), 4.87-4.76 (m, 2H), 4.58 (q, J=4.2 Hz, 1H), 3.17 (s, 1H), 0.95 (q, J=6.4 Hz, 2H), 0.71-0.62 (m, 2H); ^{19}F NMR (376 MHz, CDCl_3) δ -69.57 (s, 3F), -197.30 to -197.64 (m, 1F); LCMS m/z 585.8 (M+H) $^+$.

2) Preparation of 7c

The final target 7c was prepared from 6c (85 mg, 0.15 mmol, 1.0 eq) and potassium carbonate (60 mg, 0.44 mmol, 3.0 eq) in methanol (5 mL) according to the procedure described for the preparation of 7a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-10% methanol in dichloromethane, gradient elution) provided 42 mg (77%) of 7c as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.61 (s, 1H), 8.46 (d, J=2.0 Hz, 1H), 6.44 (dd, J=13.4, 4.7 Hz, 1H), 6.00 (d, J=4.7 Hz, 1H), 5.28 (dt, J=52.6, 4.4 Hz, 1H), 5.16-5.02 (m, 1H), 4.48 (d, J=18.9 Hz, 1H), 3.87 (q, J=5.0 Hz, 1H), 3.67 (qd, J=12.1, 6.4 Hz, 2H), 3.07 (s, 1H), 0.77 (d, J=6.7 Hz, 2H), 0.68 (d, J=4.2 Hz, 2H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -68.04 (s, 3F), -198.12 (m, 1F); LCMS m/z 377.9 (M+H) $^+$; HRMS calc for $\text{C}_{14}\text{H}_{15}\text{F}_4\text{N}_5\text{O}_3\cdot\text{H}$, 378.11838, found, 378.11873; HPLC 99.8% at 254 nm.

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(iv) Synthesis of (2R,3R,4S,5R)-5-[6-(1-cyclopropylethylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (7d)



1) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-5-[6-(cyclobutylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-tetrahydrofuran-2-yl]methyl benzoate (6e)

Intermediate 6e was prepared from 4 (100 mg, 0.18 mmol, 1.0 eq) and cyclobutylamine (0.023 mL, 0.27 mmol, 1.5 eq) in anhydrous 1,4-dioxane (3 mL) with N,N-diisopropylethylamine (0.062 mL, 0.35 mmol, 2.0 eq) as base according to the procedure described for the preparation of 6a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-50% ethyl acetate in hexanes, gradient elution) provided 90 mg (85%) of 6e as a white foam. ¹H NMR (400 MHz, CDCl₃) δ 8.17-8.05 (m, 5H), 7.71-7.41 (m, 6H), 6.63 (dd, J=22.3, 2.9 Hz, 1H), 6.15 (s, 1H), 5.78 (dd, J=17.6, 3.1 Hz, 1H), 5.37 (dd, J=50.0, 2.9 Hz, 1H), 4.89-4.73 (m, 3H), 4.57 (q, J=4.3 Hz, 1H), 2.49 (s, 2H), 2.01 (d, J=10.3 Hz, 2H), 1.81 (ddd, J=13.1, 10.1, 5.8 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ -69.63 (s, 3F), -197.30 to -197.67 (m, 1F); LCMS m/z 599.8 (M+H)⁺.

2) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-5-[6-(1-cyclopropylethylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-tetrahydrofuran-2-yl]methyl benzoate (6d)

Intermediate 6d was prepared from 4 (100 mg, 0.18 mmol, 1.0 eq) and 1-cyclopropylethylamine hydrochloride (32 mg, 0.27 mmol, 1.5 eq) in anhydrous 1,4-dioxane (3 mL) with N,N-diisopropylethylamine (0.12 mL, 0.71 mmol, 4.0 eq) as base according to the procedure described for the preparation of 6a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-50% ethyl acetate in hexanes, gradient elution) provided 106 mg (98%) of 6d as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dt, J=8.2, 1.7 Hz, 5H), 7.71-7.42 (m, 6H), 6.63 (dd, J=22.3, 2.9 Hz, 1H), 6.02 (s, 1H), 5.84-5.71 (m, 1H), 5.37 (dd, J=50.0, 2.9 Hz, 1H), 4.89-4.73 (m, 2H), 4.57 (q, J=4.1 Hz, 1H), 3.83 (s, 1H), 1.38 (dd, J=6.6, 1.0 Hz, 3H), 1.05-0.91 (m, 1H), 0.62-0.43 (m, 3H), 0.39-0.27 (m, 1H); ¹⁹F NMR (376 MHz, CDCl₃) δ 69.70 (s, 3F), -197.28 to -197.60 (m, 1F); LCMS m/z 613.8 (M+H)⁺.

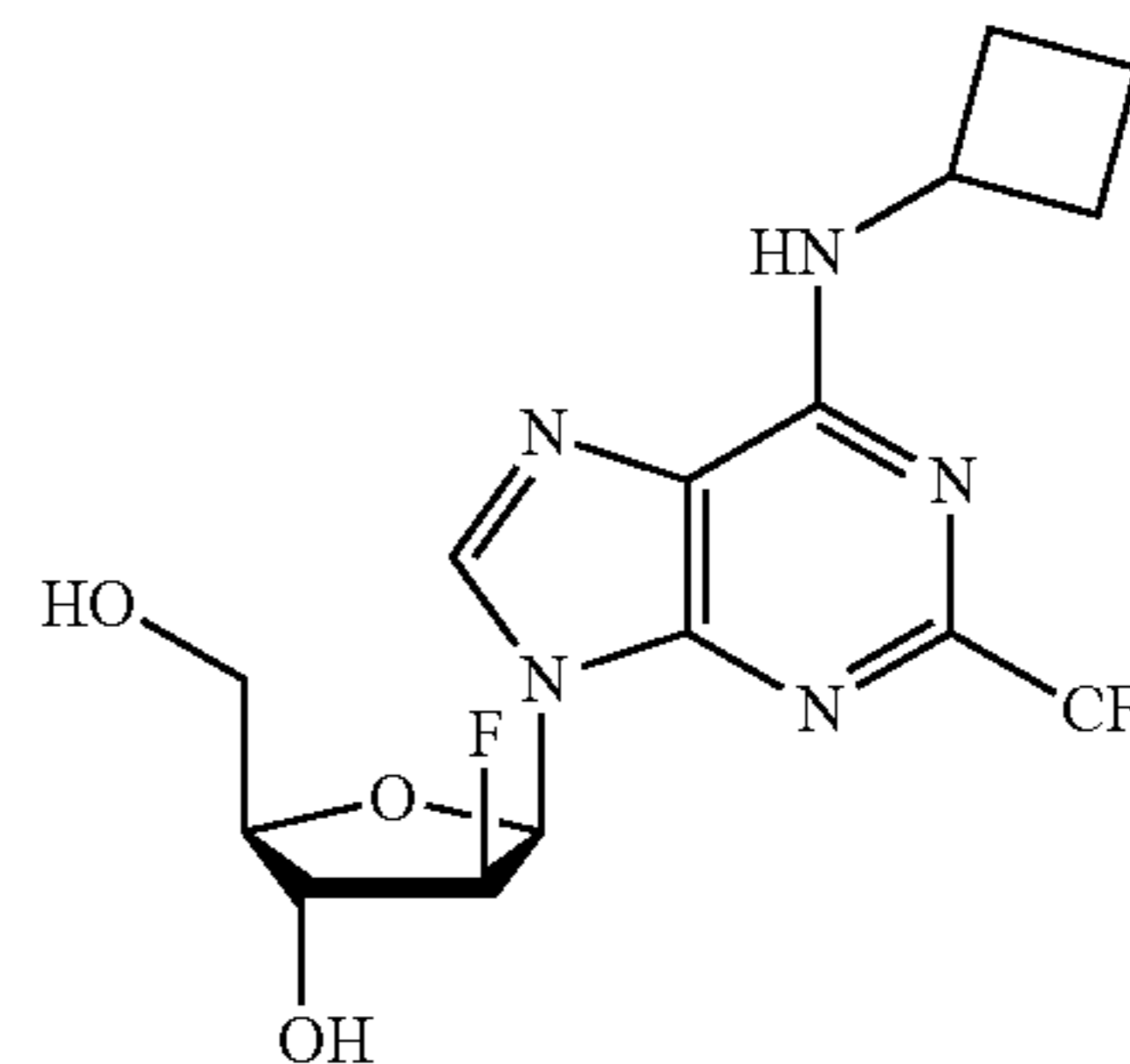
3) Preparation of 7d

The final target 7d was prepared from 6d (103 mg, 0.17 mmol, 1.0 eq) and potassium carbonate (70 mg, 0.50 mmol,

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3.0 eq) in methanol (5 mL) according to the procedure described for the preparation of 7a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-10% methanol in dichloromethane, gradient elution) provided 53 mg (75%) of 7d as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.47 (d, J=8.7 Hz, 2H), 6.43 (dd, J=13.5, 4.7 Hz, 1H), 5.98 (d, J=5.2 Hz, 1H), 5.27 (dt, J=52.6, 4.4 Hz, 1H), 5.06 (td, J=5.7, 1.7 Hz, 1H), 4.47 (dd, J=18.9, 4.8 Hz, 1H), 3.87 (q, J=5.0 Hz, 1H), 3.82-3.58 (m, 3H), 1.31 (dd, J=6.7, 2.9 Hz, 3H), 1.11 (s, 1H), 0.46 (s, 1H), 0.42-0.29 (m, 2H), 0.23 (s, 1H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -68.29 (s, 3F), -197.90 to -198.36 (m, 1F); LCMS m/z 405.8 (M+H)⁺; HRMS calc for C₁₆H₁₉F₄N₅O₃·H, 406.14968, found, 406.15056; HPLC 97.7% at 254 nm.

(v) Synthesis of (2R,3R,4S,5R)-5-[6-(cyclobutylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (7e)

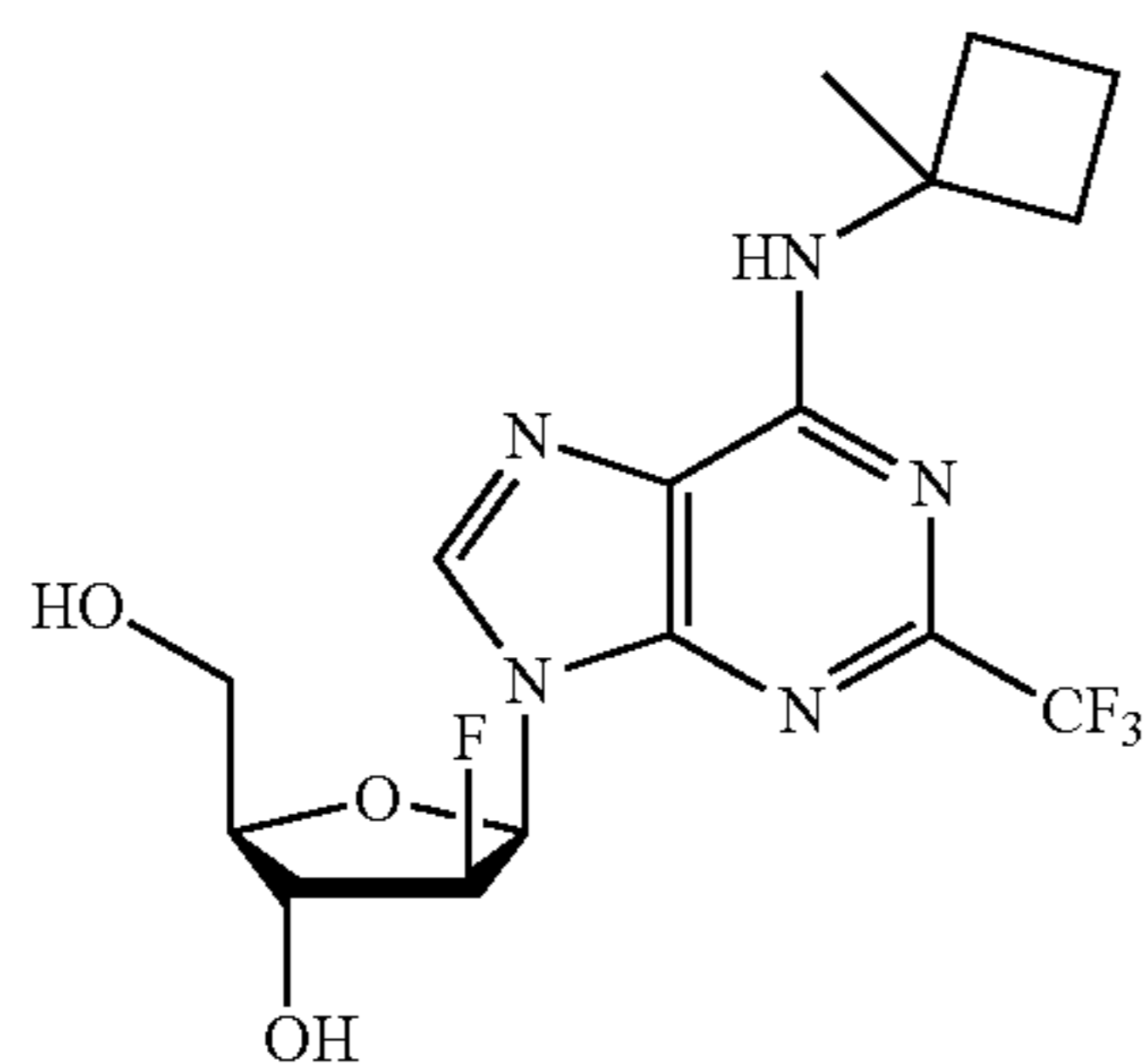


1) Preparation of 7e

The final target 7e was prepared from 6e (80 mg, 0.13 mmol, 1.0 eq) and potassium carbonate (55 mg, 0.40 mmol, 3.0 eq) in methanol (5 mL) according to the procedure described for the preparation of 7a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-10% methanol in dichloromethane, gradient elution) provided 34 mg (65%) of 7e as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (d, J=7.8 Hz, 1H), 8.47 (d, J=2.0 Hz, 1H), 6.43 (dd, J=13.5, 4.7 Hz, 1H), 5.97 (d, J=5.1 Hz, 1H), 5.27 (dt, J=52.5, 4.4 Hz, 1H), 5.06 (t, J=5.7 Hz, 1H), 4.67 (q, J=8.2 Hz, 1H), 4.47 (dq, J=19.0, 4.9 Hz, 1H), 3.87 (q, J=5.0 Hz, 1H), 3.67 (tq, J=11.8, 6.4, 5.6 Hz, 2H), 2.38-2.02 (m, 4H), 1.70 (dd, J=9.2, 5.1 Hz, 2H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -68.14 (m, 3F), -198.14 (m, 1F); LCMS m/z 391.8 (M+H)⁺; HRMS calc for C₁₅H₁₇F₄N₅O₃·H, 392.13043, found, 392.13334; HPLC 99.8% at 254 nm.

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(vi) Synthesis of (2R,3R,4S,5R)-4-fluoro-2-(hydroxymethyl)-5-[6-[(1-methylcyclobutyl)amino]-2-(trifluoromethyl)purin-9-yl]tetrahydrofuran-3-ol (7f)



1) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-4-fluoro-5-[6-[(1-methylcyclobutyl)amino]-2-(trifluoromethyl)purin-9-yl]tetrahydrofuran-2-yl]methyl benzoate (6f)

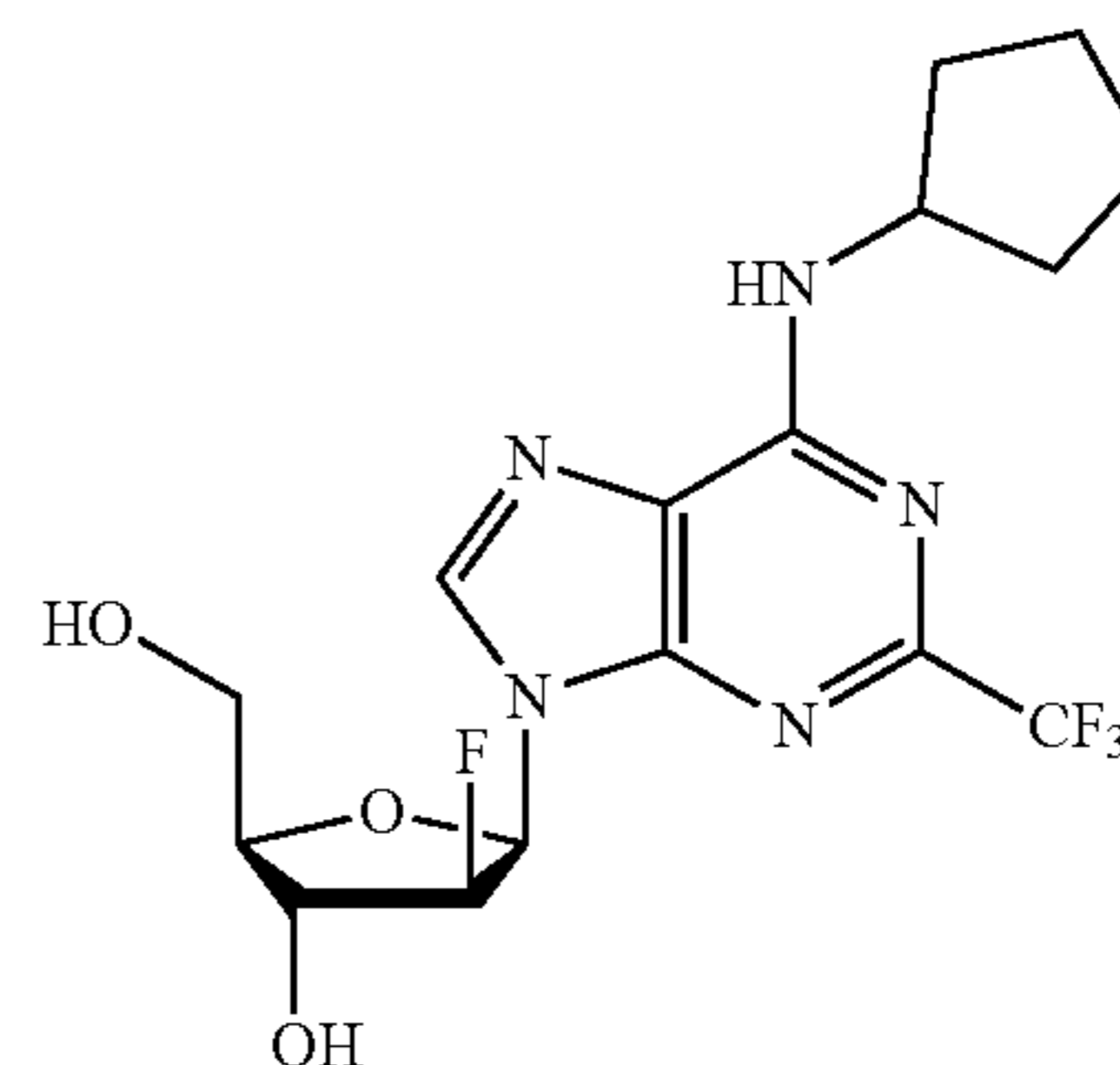
Intermediate 6f was prepared from 4 (100 mg, 0.18 mmol, 1.0 eq) and 1-methylcyclobutanamine hydrochloride (32 mg, 0.27 mmol, 1.5 eq) in anhydrous 1,4-dioxane (3 mL) with N,N-diisopropylethylamine (0.12 mL, 0.71 mmol, 4.0 eq) as base according to the procedure described for the preparation of 6a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-50% ethyl acetate in hexanes, gradient elution) provided 106 mg (98%) of 6f as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.16-8.06 (m, 5H), 7.71-7.41 (m, 6H), 6.63 (dd, J=22.3, 2.9 Hz, 1H), 6.12 (s, 1H), 5.78 (dd, J=17.6, 3.1 Hz, 1H), 5.48-5.27 (m, 1H), 4.90-4.75 (m, 2H), 4.57 (q, J=4.2 Hz, 1H), 2.47 (q, J=10.0 Hz, 2H), 2.19 (d, J=10.6 Hz, 2H), 1.99-1.84 (m, 2H), 1.66 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -69.83 (s, 3F), -197.28 to -197.59 (m, 1F); LCMS m/z 613.8 (M+H)⁺.

2) Preparation of 7f

The final target 7f was prepared from 6f (100 mg, 0.13 mmol, 1.0 eq) and potassium carbonate (68 mg, 0.49 mmol, 3.0 eq) in methanol (5 mL) according to the procedure described for the preparation of 7a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-10% methanol in dichloromethane, gradient elution) provided 11 mg (16%) of 7f as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.56 (s, 1H), 8.44 (d, J=2.0 Hz, 1H), 6.42 (dd, J=13.5, 4.7 Hz, 1H), 5.98 (d, J=5.0 Hz, 1H), 5.26 (ddd, J=52.6, 4.8, 4.1 Hz, 1H), 5.06 (t, J=5.7 Hz, 1H), 4.47 (dq, J=19.0, 4.8 Hz, 1H), 3.87 (tdd, J=5.2, 4.1, 0.8 Hz, 1H), 3.67 (tq, J=11.8, 6.4, 5.6 Hz, 2H), 2.41 (q, J=10.1 Hz, 2H), 2.10 (s, 2H), 1.92-1.74 (m, 2H), 1.57 (s, 3H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -68.49 (s, 3F), -198.15 (m, 1F); LCMS m/z 405.8 (M+H)⁺; HRMS calc for C₁₆H₁₉F₄N₅O₃·H, 406.14968, found, 406.1505; HPLC 97.2% at 254 nm.

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(vii) Synthesis of (2R,3R,4S,5R)-5-[6-(cyclopentylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol (7g)



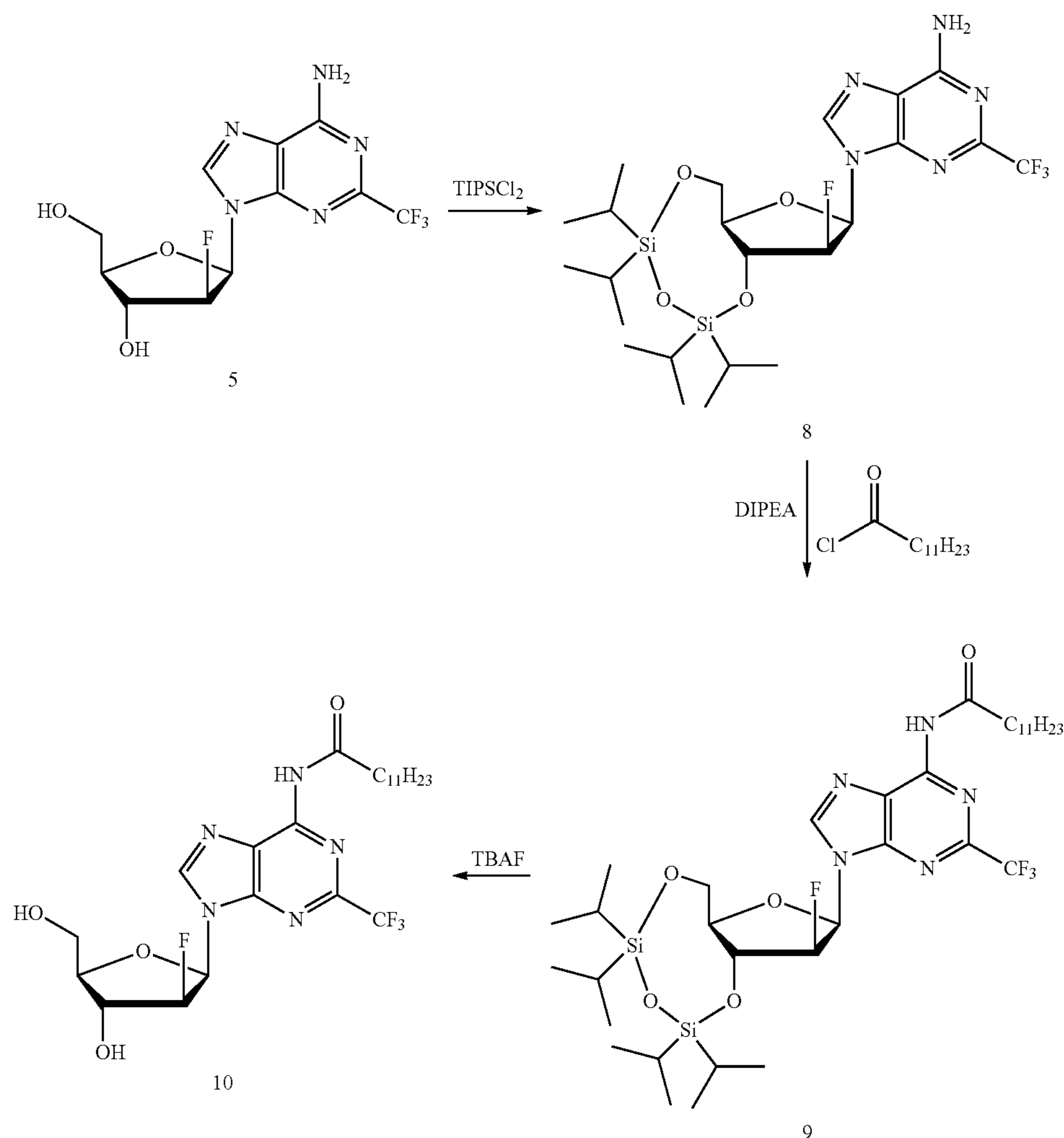
1) Preparation of [(2R,3R,4S,5R)-3-benzoyloxy-5-[6-(cyclopentylamino)-2-(trifluoromethyl)purin-9-yl]-4-fluoro-tetrahydrofuran-2-yl]methyl benzoate (6g)

Intermediate 6g was prepared from 4 (100 mg, 0.18 mmol, 1.0 eq) and cyclopentylamine (0.026 mL, 0.27 mmol, 1.5 eq) in anhydrous 1,4-dioxane (3 mL) with N,N-diisopropylethylamine (0.062 mL, 0.35 mmol, 2.0 eq) as base according to the procedure described for the preparation of 6a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-50% ethyl acetate in hexanes, gradient elution) provided 93 mg (86%) of 6g as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.17-8.05 (m, 5H), 7.69-7.64 (m, 1H), 7.61-7.56 (m, 1H), 7.55-7.50 (m, 2H), 7.48-7.43 (m, 2H), 6.64 (dd, J=22.3, 2.9 Hz, 1H), 6.02 (s, 1H), 5.78 (dd, J=17.5, 3.0 Hz, 1H), 5.47-5.28 (m, 1H), 4.88-4.75 (m, 2H), 4.62 (s, 1H), 4.60-4.55 (m, 1H), 2.16 (dq, J=12.4, 6.4 Hz, 2H), 1.84-1.68 (m, 4H), 1.56 (dq, J=13.4, 6.7 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ -69.65 (s, 3F), -197.50 (m, 1F); LCMS m/z 613.8 (M+H)⁺.

2) Preparation of 7g

The final target 7g was prepared from 6g (90 mg, 0.15 mmol, 1.0 eq) and potassium carbonate (61 mg, 0.44 mmol, 3.0 eq) in methanol (5 mL) according to the procedure described for the preparation of 7a to afford a residue. Purification by flash chromatography (12 g gold silica column, 0-10% methanol in dichloromethane, gradient elution) provided 34 mg (58%) of 7g as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.50-8.41 (m, 2H), 6.43 (dd, J=13.5, 4.7 Hz, 1H), 5.98 (d, J=5.1 Hz, 1H), 5.27 (d, J=53.2 Hz, 1H), 5.06 (t, J=5.7 Hz, 1H), 4.47 (dq, J=19.0, 5.0 Hz, 2H), 3.87 (q, J=5.0 Hz, 1H), 3.67 (qd, J=12.4, 11.8, 6.4 Hz, 2H), 1.97 (s, 2H), 1.80-1.49 (m, 6H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -68.14 (m, 3F), -197.96 to -198.31 (m, 1F); LCMS m/z 405.9 (M+H)⁺; HRMS calc for C₁₆H₁₉F₄N₅O₃·H, 406.14968, found, 406.14985; HPLC 97.7% at 254 nm.

C. Procedure for the Synthesis of
2'-deoxy-2'-fluoroarabinosyl nucleoside prodrug
(10)



(i) Preparation of 9-[(6aR,8R,9S,9aR)-9-fluoro-2,2,4,4-tetraisopropyl-6a,8,9,9a-tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl]-2-(trifluoromethyl)purin-6-amine (8)

To a solution of the nucleoside 5 (376 mg, 1.11 mmol, 1.0 eq) in anhydrous pyridine (5 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (0.39 mL, 1.23 mmol, 1.1 eq). The reaction mixture was stirred at 20° C. for 18 hrs under argon. The reaction mixture was evaporated under reduced pressure to afford a white solid, which was dissolved in dichloromethane (75 mL), washed with saturated aqueous NaHCO₃ (2×25 mL), saturated aqueous NH₄Cl (2×25 mL) and brine (25 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and filtered. The filtrate was evaporated under reduced pressure to give a colorless oil, which was purified by flash chromatography (24 g silica column, 0-50% ethyl acetate in hexanes, gradient elution) to provide 0.46 g (71%) of 8 as a white foam. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, J=2.2 Hz, 1H), 6.45 (dd, J=11.8, 5.0 Hz, 1H), 5.93 (s, 2H), 5.38-5.18 (m, 1H), 4.75

(ddd, J=22.9, 7.1, 4.6 Hz, 1H), 4.16-4.04 (m, 2H), 3.91 (dddd, J=7.1, 5.3, 3.7, 1.0 Hz, 1H), 1.17-1.05 (m, 28H); ¹⁹F NMR (376 MHz, CDCl₃) δ -69.55 (s, 3F), -196.32 (m, 1F); LCMS m/z 579.8 (M+H)⁺.

(ii) Preparation of N-[9-[(6aR,8R,9S,9aR)-9-fluoro-2,2,4,4-tetraisopropyl-6a,8,9,9a-tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl]-2-(trifluoromethyl)purin-6-yl]dodecanamide (9)

To a solution of intermediate 8 (100 mg, 0.17 mmol, 1.0 eq) in anhydrous dichloromethane (3 mL) was added N,N-diisopropylethylamine (0.03 mL, 0.19 mmol, 1.1 eq) followed by dodecanoyl chloride (0.05 mL, 0.19 mmol, 1.1 eq). The reaction mixture was irradiated at 120° C. for 2 hrs in a microwave reactor. The reaction mixture was evaporated under reduced pressure to afford a brown oil, which was purified by flash chromatography (12 g gold silica column, 0-20% ethyl acetate in hexanes, gradient elution) to provide 30 mg (23%) of 9 as a brown oil. LCMS m/z 761.8 (M+H)⁺.

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(iii) Preparation of N-[9-[(2R,3S,4R,5R)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-2-(trifluoromethyl)purin-6-yl]dodecanamide (10)

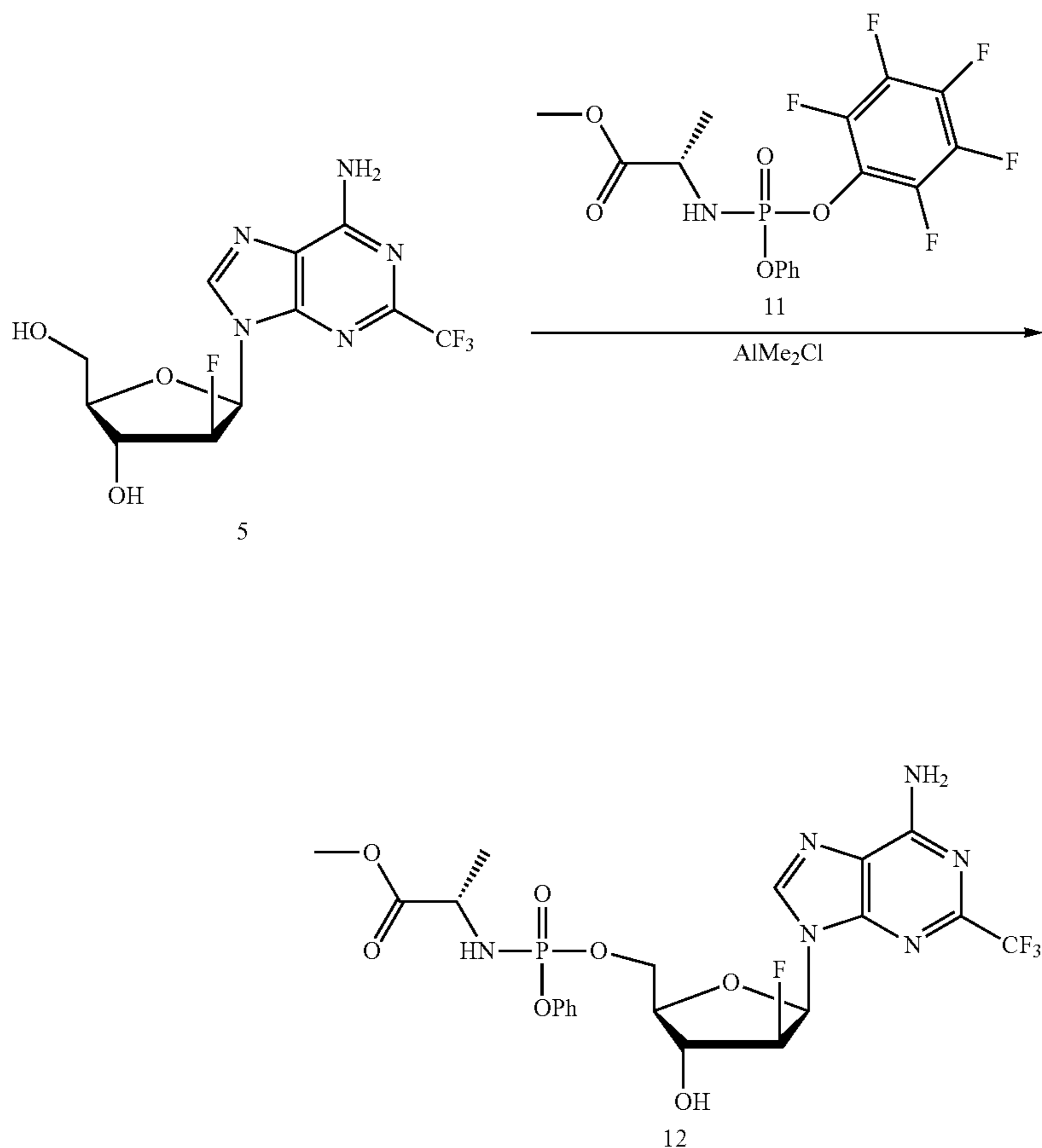
To a solution of intermediate 9 (57 mg, 0.07 mmol) in anhydrous tetrahydrofuran (4 mL) was added 1M solution of tetrabutylammonium fluoride (0.16 mL, 0.16 mmol, 2.1 eq) in tetrahydrofuran. The reaction mixture was stirred at room temperature for 18 hrs under argon. The reaction mixture was evaporated under reduced pressure to afford a crude product, which was purified by flash chromatography (12 g gold silica column, 0-10% methanol in dichloromethane, gradient elution) to provide 23 mg (59%) of 10 as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 11.12 (s, 1H), 8.79 (d, J=1.9 Hz, 1H), 6.56 (dd, J=12.9, 4.7 Hz, 1H), 6.02 (d, J=5.2 Hz, 1H), 5.44-5.24 (m, 1H), 5.10 (t, J=5.7 Hz, 1H), 4.50 (dq, J=19.1, 4.9 Hz, 1H), 3.95-3.86 (m, 1H), 3.77-3.62 (m, 2H), 2.59 (t, J=7.4 Hz, 2H), 1.61 (p, J=7.2 Hz, 2H), 1.36-1.20 (m, 16H), 0.88-0.81 (m, 3H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -67.54 (s, 3F), -197.98 (m, 1F); LCMS m/z 519.9 (M+H)⁺; HRMS calc for C₂₃H₃₃F₄N₅O₄·H, 520.25414, found, 520.25382; HPLC 99.8% at 254 nm.

d. Procedure for the Synthesis of 2'-deoxy-2'-fluoroarabinosyl nucleotide protide (12)

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(i) Preparation of methyl (2S)-2-[[phenoxy-[[rac-(2R,3R,4S,5R)-5-[6-amino-2-(trifluoromethyl)purin-9-yl]-4-fluoro-3-hydroxy-tetrahydrofuran-2-yl]methoxy]phosphoryl]amino]propanoate (12)

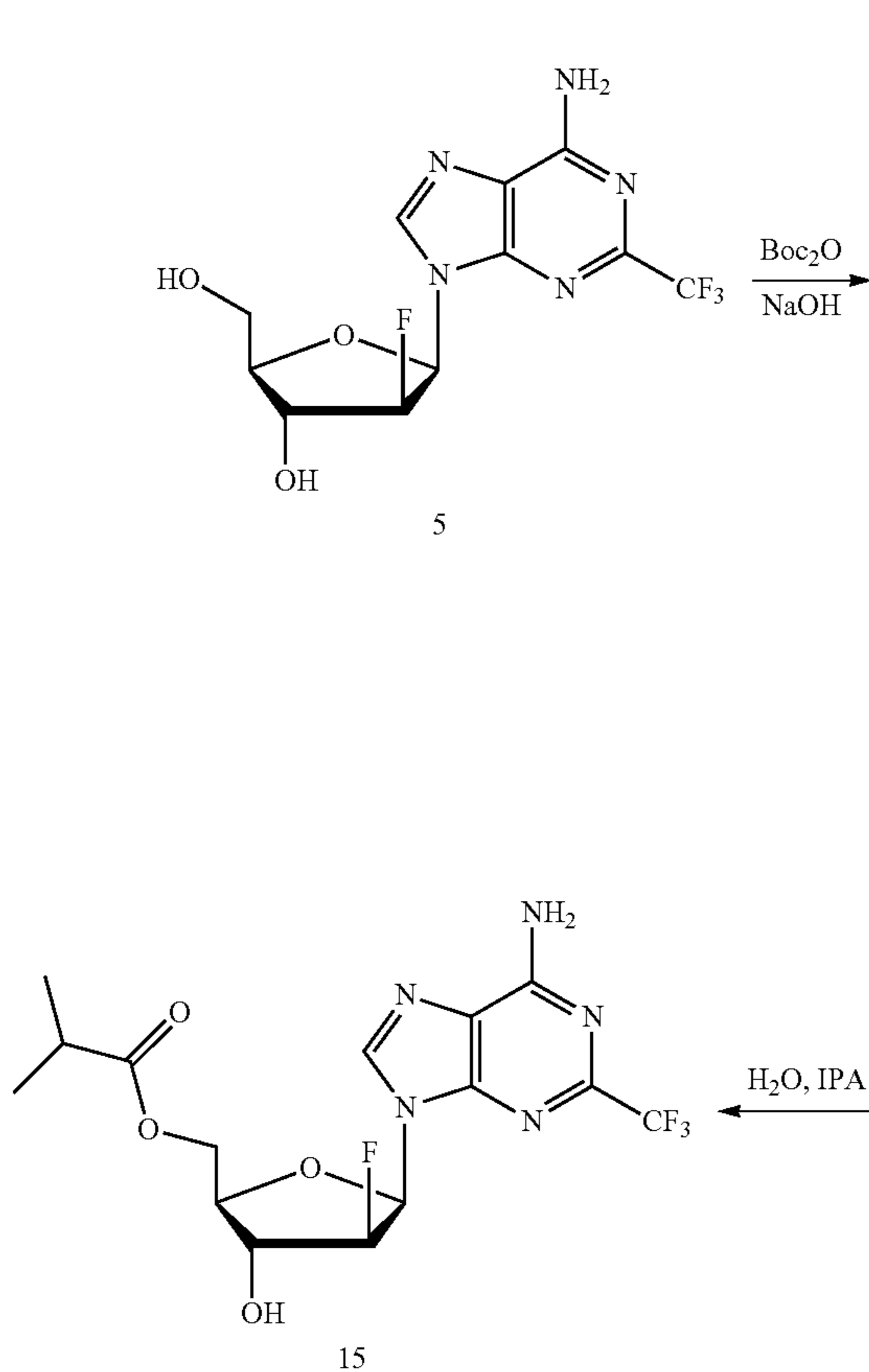
To an oven dried round-bottom flask was added the nucleoside 5 (100 mg, 0.30 mmol, 1.0 eq). Residual water was removed by co-evaporation with anhydrous pyridine (3 mL) under reduced pressure at 40° C. This was repeated twice with a fresh portion of anhydrous pyridine (3 mL) each time. The nucleoside 5 was dissolved in anhydrous pyridine (1.5 mL) and then the phosphoramidate 11 (151 mg, 0.36 mmol, 1.2 eq) was added. The solution was cooled to 0° C. in an ice-water bath and then a 1M solution of dimethyl aluminum chloride (0.15 mL, 0.15 mmol, 0.5 eq) was added. The reaction mixture was allowed to warm to room temperature and stirred for 5 days under argon. The reaction mixture was evaporated under reduced pressure to afford a residue, which was purified by flash chromatography (12 g silica column, 0-10% methanol in dichloromethane, gradient elution) to provide 42 mg (24%) of 12 as a white solid as a single diastereomer. ¹H NMR (400 MHz, DMSO-d₆) δ 8.39 (d, J=2.1 Hz, 1H), 8.03 (d, J=2.6 Hz, 2H), 7.35 (dt, J=8.9, 7.3 Hz, 2H), 7.24-7.09 (m, 3H), 6.48 (ddd, J=14.2, 6.7, 4.7 Hz, 1H), 6.25-5.99 (m, 2H), 5.32 (dq, J=52.4, 4.4 Hz, 1H), 4.57



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(dt, $J=18.9, 4.7$ Hz, 1H), 4.29 (ddd, $J=25.3, 12.3, 5.5$ Hz, 2H), 4.18-4.02 (m, 1H), 3.93-3.73 (m, 1H), 3.56 (d, $J=11.2$ Hz, 3H), 1.27-1.12 (m, 3H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -68.07 (s, 3F), -197.88 (m, 1F); ^{31}P NMR (162 MHz, DMSO- d_6) δ 3.65; LCMS m/z 579.1 (M+H) $^+$; HRMS calc for $\text{C}_{21}\text{H}_{23}\text{F}_4\text{N}_6\text{O}_7\text{P}\cdot\text{H}$, 579.13747, found, 579.1378; HPLC 95.6% at 254 nm.

e. Procedure for the Synthesis of [(2R,3R,4S,5R)-5-[6-amino-2-(trifluoromethyl)purin-9-yl]-4-fluoro-3-hydroxy-tetrahydrofuran-2-yl]methyl 2-methylpropanoate (15)



(i) Preparation of tert-butyl [(2R,3R,4S,5R)-5-[6-amino-2-(trifluoromethyl)purin-9-yl]-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-yl] carbonate (13)

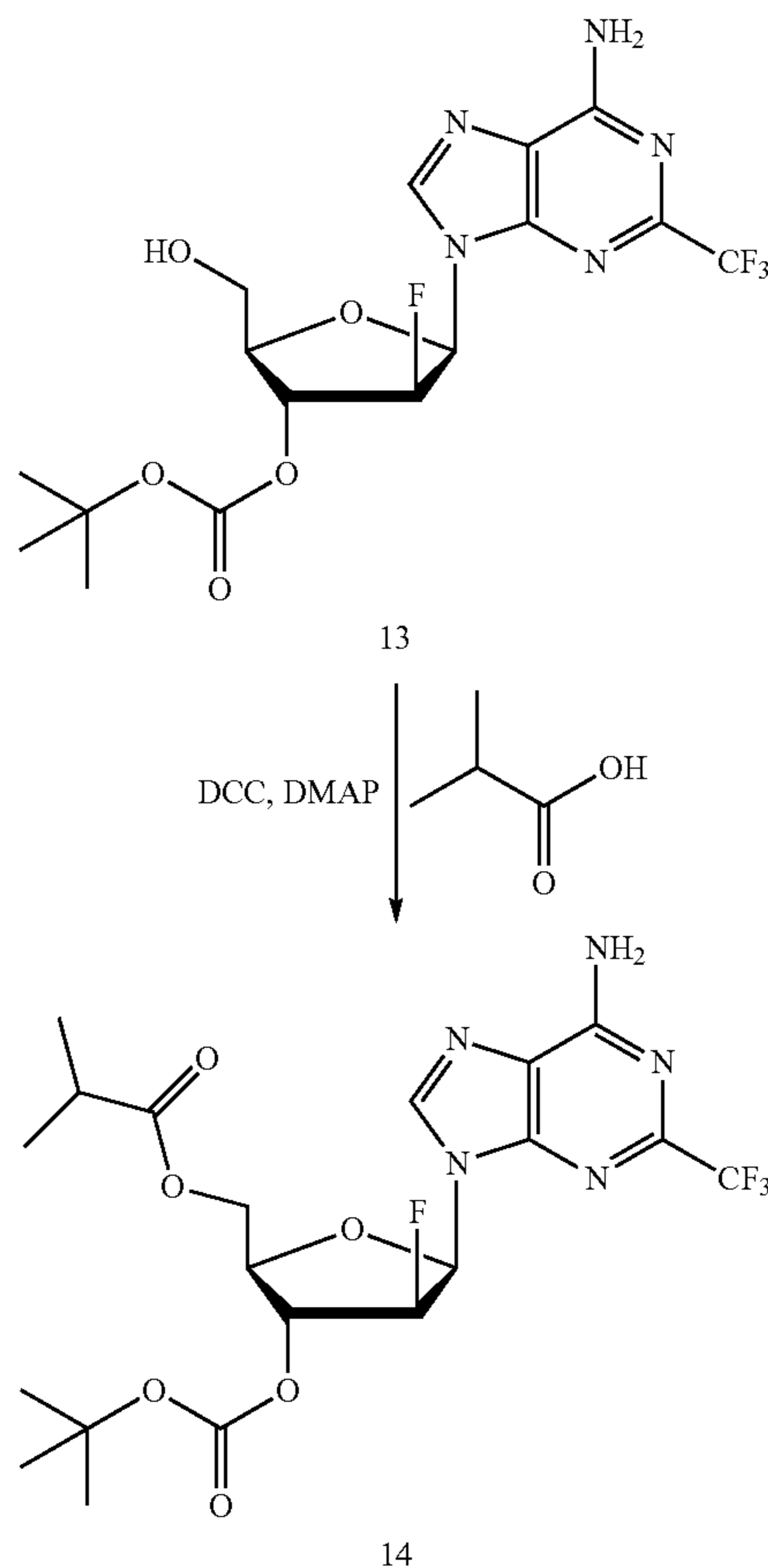
A solution of the nucleoside 5 (250 mg, 0.74 mmol, 1.0 eq) and sodium hydroxide (59 mg, 1.48 mmol, 2.0 eq) in tetrahydrofuran (4 mL) and water (1 mL) was treated with di-tert-butyl dicarbonate (176 mg, 0.81 mmol, 1.1 eq) and the resulting mixture was stirred at room temperature for 18 hrs under argon. The reaction mixture was evaporated under reduced pressure, extracted with ethyl acetate, dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude product was purified by flash chromatography (12 g silica column, 0-15% methanol in dichloromethane, gradient elution) to provide 210 mg (65%) of 13 as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.45 (d, $J=2.5$ Hz, 1H), 8.03

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(s, 2H), 6.42 (dd, $J=16.5, 4.4$ Hz, 1H), 5.57 (ddd, $J=50.9, 4.4, 2.8$ Hz, 1H), 5.39 (ddd, $J=18.9, 5.2, 2.9$ Hz, 1H), 5.13 (t, $J=5.9$ Hz, 1H), 4.08 (q, $J=4.8$ Hz, 1H), 3.69 (dq, $J=15.7, 6.8, 6.3$ Hz, 2H), 1.45 (s, 9H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -68.03 (s, 3F), -197.78 to -198.09 (m, 1F); LCMS m/z 437.9 (M+H) $^+$.

(ii) Preparation of [(2R,3R,4S,5R)-5-[6-amino-2-(trifluoromethyl)purin-9-yl]-3-tert-butoxycarbonyloxy-4-fluoro-tetrahydrofuran-2-yl]methyl 2-methylpropanoate (14)

To a cold solution of the intermediate 13 (120 mg, 0.27 mmol, 1.0 eq), isobutyric acid (0.03 mL, 0.33 mmol, 1.2 eq)



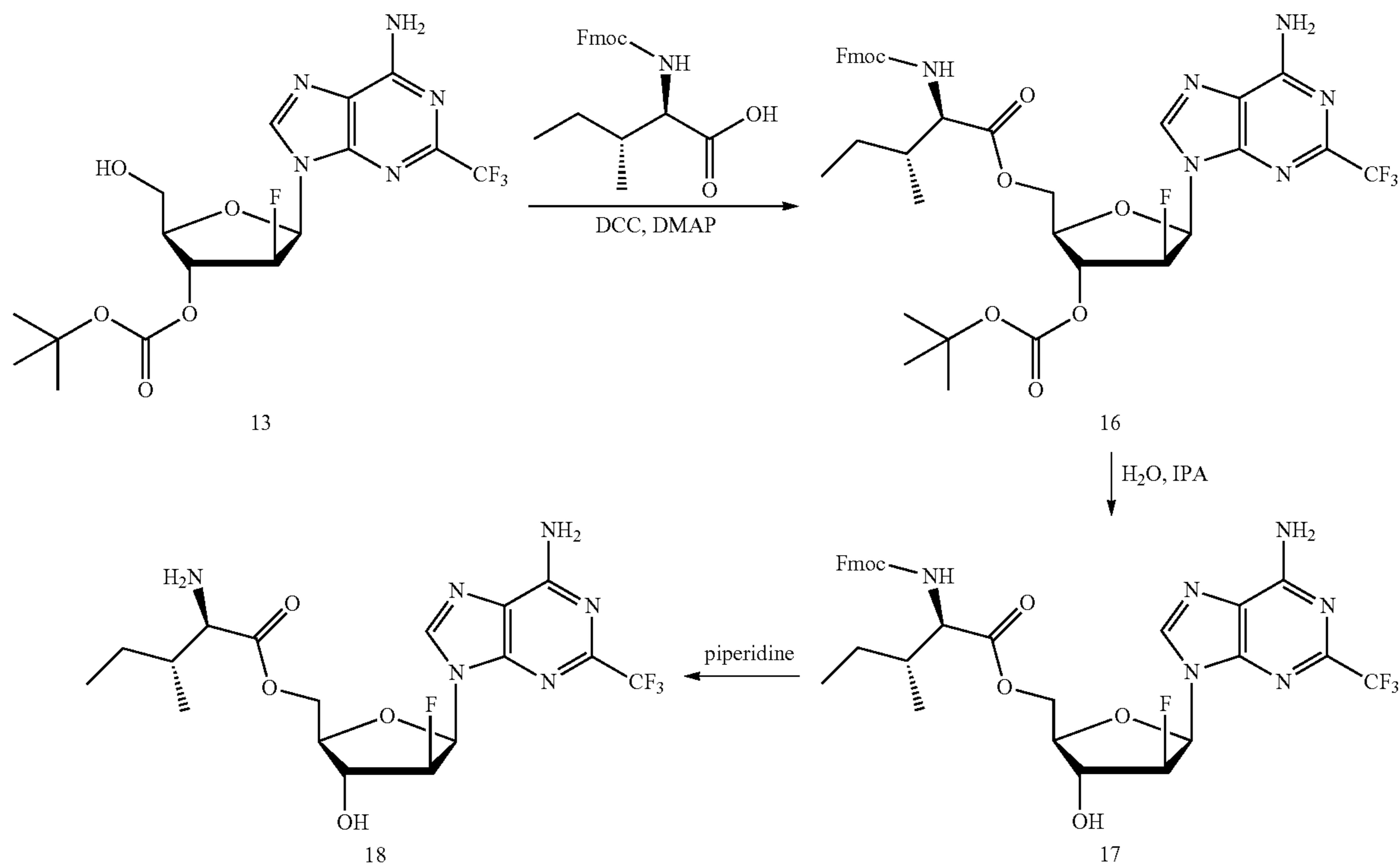
and 4-dimethylaminopyridine (2.7 mg, 0.020 mmol, 0.08 eq) in anhydrous dichloromethane (3 mL) under argon atmosphere was added N,N -dicyclohexylcarbodiimide (68 mg, 0.33 mmol, 1.2 eq). The reaction mixture was stirred for 18 hrs till room temperature, then filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g silica column, 0-100% ethyl acetate in hexanes, gradient elution) to provide 100 mg (72%) of 14 as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 8.37 (d, $J=2.3$ Hz, 1H), 8.04 (s, 2H), 6.46 (dd, $J=15.2, 4.7$ Hz, 1H), 5.72-5.49 (m, 2H), 4.45-4.25 (m, 3H), 2.54 (p, $J=7.0$ Hz, 1H), 1.44 (s, 9H), 1.07 (dd, $J=7.0, 0.8$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -68.11 (s, 3F), -198.41 (m, 1F); LCMS m/z 507.9 (M+H) $^+$.

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(iii) Preparation of 15

A solution of the intermediate 14 (100 mg, 0.20 mmol, 1.0 eq) in isopropanol (2 mL) and water (2 mL) was heated at 90° C. for 5 hrs with stirring. The reaction mixture was cooled to room temperature and evaporated to dryness. The residue was partitioned between ethyl acetate and water, and the organic layer was dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (12 g silica column, 0-15% methanol in dichloromethane, gradient elution) to provide 37 mg (46%) of 15 as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.36 (d, J=2.1 Hz, 1H), 8.01 (s, 2H), 6.45 (dd, J=13.7, 4.8 Hz, 1H), 6.15 (s, 1H), 5.30 (dt, J=52.5, 4.4 Hz, 1H), 4.56 (dt, J=19.1, 4.9 Hz, 1H), 4.33 (qd, J=12.1, 5.2 Hz, 2H), 4.04 (td, J=6.1, 3.5 Hz, 1H), 2.55 (p, J=7.0 Hz, 1H), 1.06 (dd, J=7.0, 1.0 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -68.08 (s, 3F), -198.16 (m, 1F); LCMS m/z 407.9 (M+H)⁺; HRMS calc for C₁₅H₁₇F₄N₅O₄·H, 408.12894, found, 408.12915; HPLC 99.8% at 254 nm.

f. Procedure for the Synthesis of [(2R,3R,4S,5R)-5-[6-amino-2-(trifluoromethyl)purin-9-yl]-4-fluoro-3-hydroxy-tetrahydrofuran-2-yl]methyl (2R,3R)-2-amino-3-methyl-pentanoate (18)



(i) Preparation of [(2R,3R,4S,5R)-5-[6-amino-2-(trifluoromethyl)purin-9-yl]-3-tert-butoxycarbonyloxy-4-fluoro-tetrahydrofuran-2-yl]methyl (2R,3R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methyl-pentanoate (16)

Intermediate 16 was prepared from 13 (95 mg, 0.22 mmol, 1.0 eq), Fmoc-D-isoleucine (92 mg, 0.26 mmol, 1.2 eq), 4-dimethylaminopyridine (2.1 mg, 0.020 mmol, 0.08 eq) and N,N-dicyclohexylcarbodiimide (54 mg, 0.26 mmol,

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1.2 eq) in anhydrous dichloromethane (3 mL) according to the procedure described for the preparation of 14 to afford a residue. Purification by flash chromatography (12 g silica column, 0-100% ethyl acetate in hexanes, gradient elution) provided 125 mg (74%) of 16 as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.38 (d, J=2.5 Hz, 1H), 8.03 (s, 2H), 7.86 (d, J=7.6 Hz, 2H), 7.79 (d, J=8.2 Hz, 1H), 7.70 (t, J=8.6 Hz, 2H), 7.38 (td, J=7.4, 4.3 Hz, 2H), 7.28 (t, J=7.4 Hz, 2H), 6.44 (dd, J=16.4, 4.4 Hz, 1H), 5.62 (dt, J=51.0, 3.6 Hz, 1H), 5.47 (ddd, J=18.9, 5.4, 3.1 Hz, 1H), 4.44 (t, J=3.3 Hz, 2H), 4.36-4.15 (m, 4H), 4.01 (d, J=7.2 Hz, 1H), 1.97 (s, 2H), 1.44 (s, 9H), 1.15 (t, J=7.1 Hz, 2H), 0.82 (d, J=6.8 Hz, 3H), 0.76 (t, J=7.4 Hz, 2H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -68.07 (s, 3F), -198.08 (m, 1F); LCMS m/z 772.8 (M+H)⁺.

(ii) Preparation of [(2R,3R,4S,5R)-5-[6-amino-2-(trifluoromethyl)purin-9-yl]-4-fluoro-3-hydroxy-tetrahydrofuran-2-yl]methyl (2R,3R)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-methyl-pentanoate (17)

Intermediate 17 was prepared from 16 (125 mg, 0.16 mmol, 1.0 eq) in isopropanol (1.5 mL) and water (1.5 mL) according to the procedure described for the preparation of

15. 85 mg (78%) of crude 17 was obtained as a white solid and used in the next step without further purification. LCMS m/z 672.9 (M+H)⁺.

(iii) Preparation of 18

To a solution of intermediate 17 (85 mg, 0.13 mmol, 1.0 eq) in anhydrous N,N-dimethylformamide (2 mL) was added piperidine (0.03 mL, 0.32 mmol, 2.5 eq) and the reaction mixture was stirred under argon for 30 mins. The

reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (12 g gold silica column, 0-20% methanol in dichloromethane, gradient elution) to provide 37 mg (63%) of 18 as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.35 (d, J=2.2 Hz, 1H), 8.01 (s, 2H), 6.45 (dd, J=14.7, 4.6 Hz, 1H), 6.16 (d, J=4.1 Hz, 1H), 5.29 (dt, J=52.4, 4.2 Hz, 1H), 4.54 (d, J=18.5 Hz, 1H), 4.41-4.31 (m, 2H), 4.07 (q, J=5.4 Hz, 1H), 3.18 (d, J=5.5 Hz, 1H), 1.69 (s, 2H), 1.55 (dq, J=12.7, 5.8 Hz, 1H), 1.36 (ddd, J=13.4, 7.4, 4.5 Hz, 1H), 1.07 (ddd, J=13.3, 8.7, 7.0 Hz, 1H), 0.79 (d, J=6.8 Hz, 3H), 0.74 (t, J=7.4 Hz, 3H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -68.08 (s, 3F), -197.82 (m, 1F); LCMS m/z 450.9 (M+H)⁺; HRMS calc for C₁₇H₂₂F₄N₆O₄·H, 451.17114, found, 451.17211; HPLC 96.8% at 254 nm.

2. In Vitro Determination of IC₅₀

Select tumor lines representative of triple negative breast cancer (MDA-MB-231 and BT549) were identified for testing of efficacy of compounds. Assessment of compound efficacy was determined by a test of cell viability after 72-hour incubation with compound using CellTiter-Glo 2.0 (Promega). A compound was considered effective if it

achieved the following criterion: 50% viability was seen at a concentration less than or equal to 5 μM of compound; efficacy in MDA-MB-231 or BT549; and either no effect on viability in the normal epithelial lines, or a selectivity index of >2. Selectivity index is defined as the ratio of the calculated IC₅₀ in normal epithelial lines to the calculated IC₅₀ in a cancerous cell line. For CellTiter-Glo cells are plated in a 96-well, opaque, flat-bottomed black plate. Cells are seeded at 5,000 cells per well and allowed to incubate for 6 hours to allow for attachment. Cells are then dosed in a 12-point serial dilution spanning a range of 50 μM to 25 nM. Clofarabine is used as a positive control for all cell lines, and each plate contains media only, and DMSO controls as negatives for each compound tested. Final volume for both cells and compound should be 100 uL. After 72-hour exposure to compound, plates are removed from the incubator and allowed to equilibrate to room temperature for 30 minutes. An equal volume of CellTiter-Glo 2.0 reagent is added to media present in well (100 uL). Plates are then placed onto an orbital shaker and allow to incubate while shaking for 10 to 15 minutes. Raw luminescence readings are obtained. Log transformations of the background subtracted data are analyzed using a 4PL-fit model, and IC₅₀ values are calculated based on the sigmoidal fit of the non-linear regression model.

TABLE 1

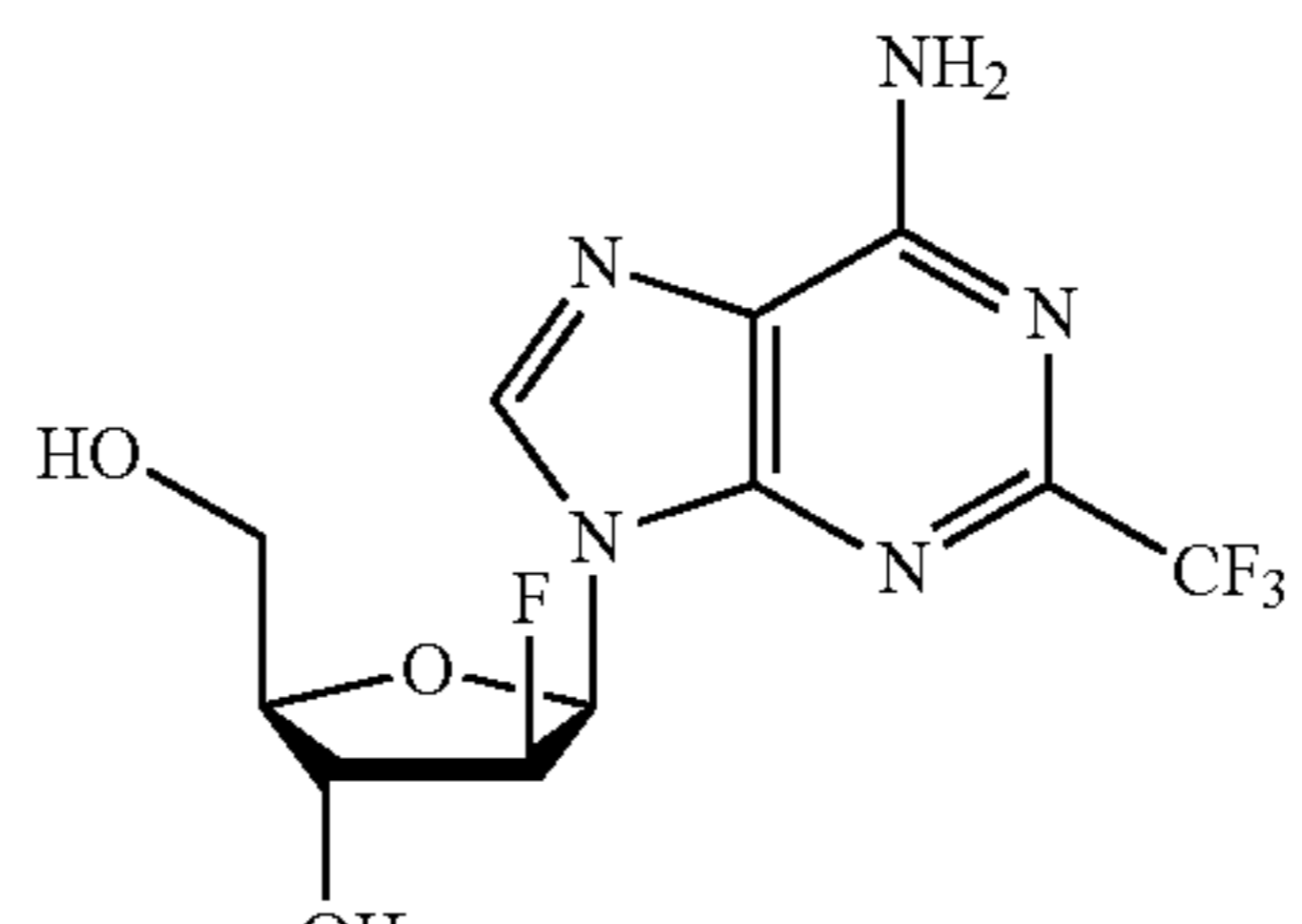
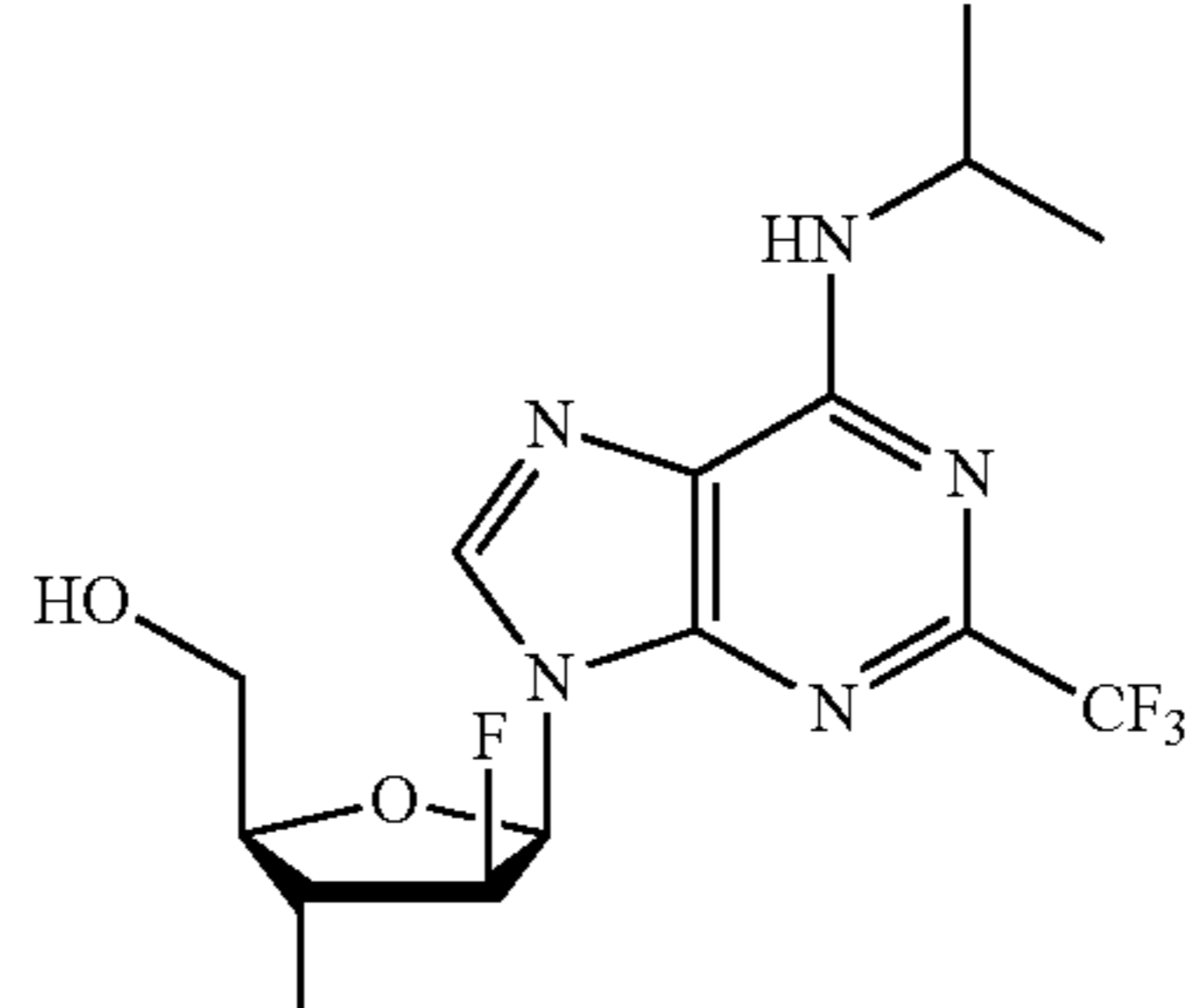
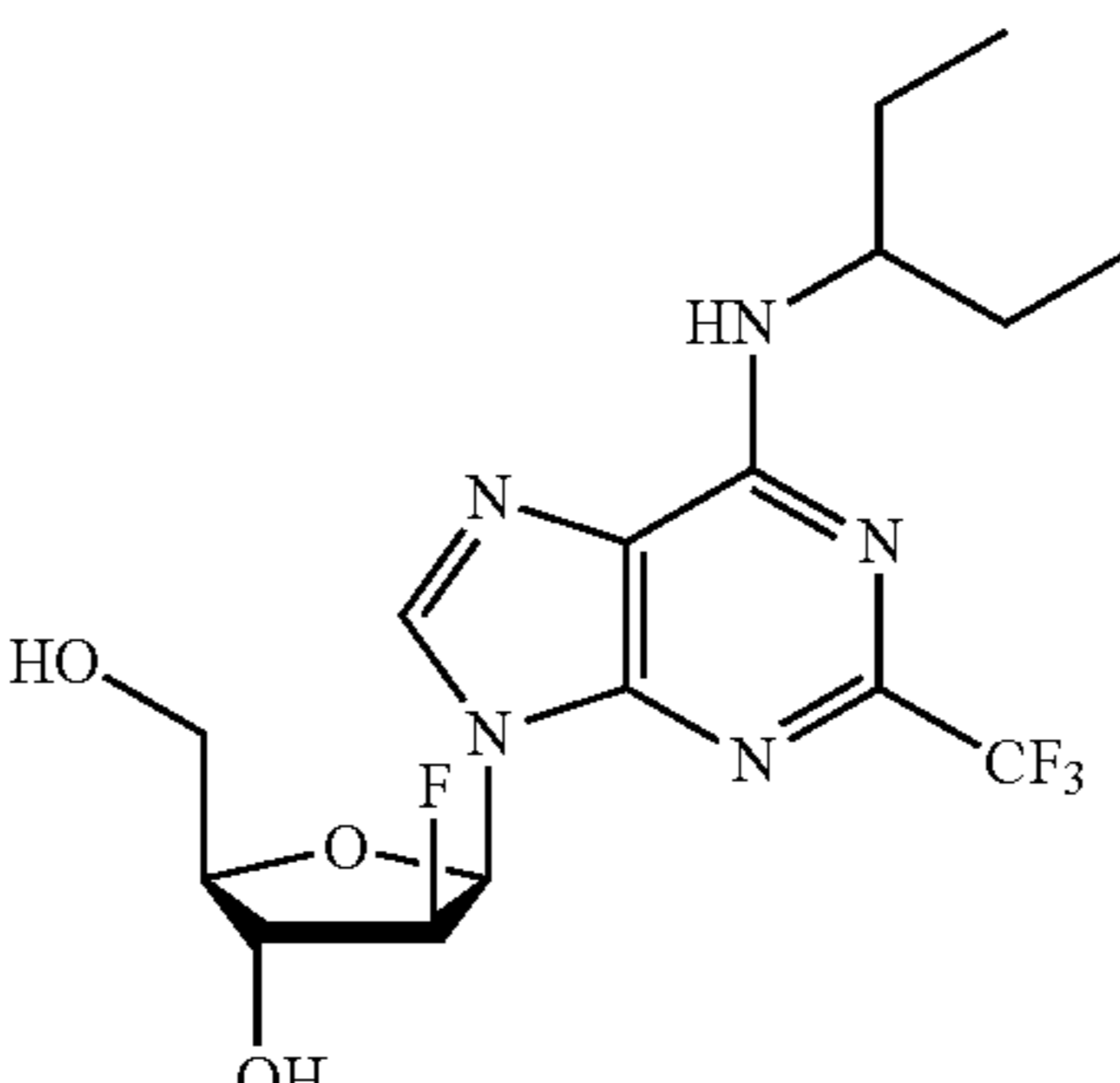
Compound	Structure	IC ₅₀ (μM)	
		MDA-MB-231	BT549
5		4.16	0.018
7a		20.54	Not determined
7b		66.99	>50

TABLE 1-continued

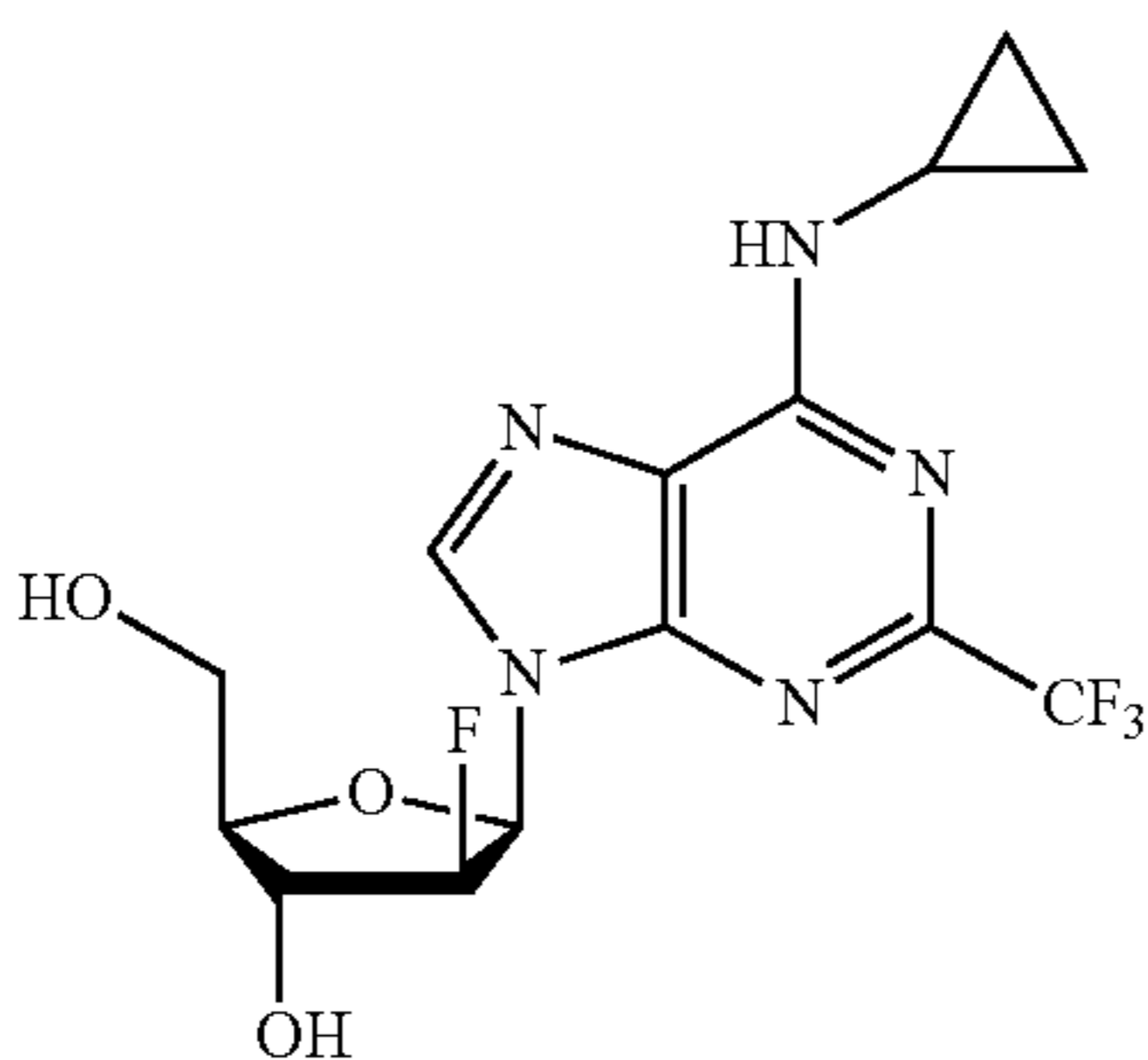
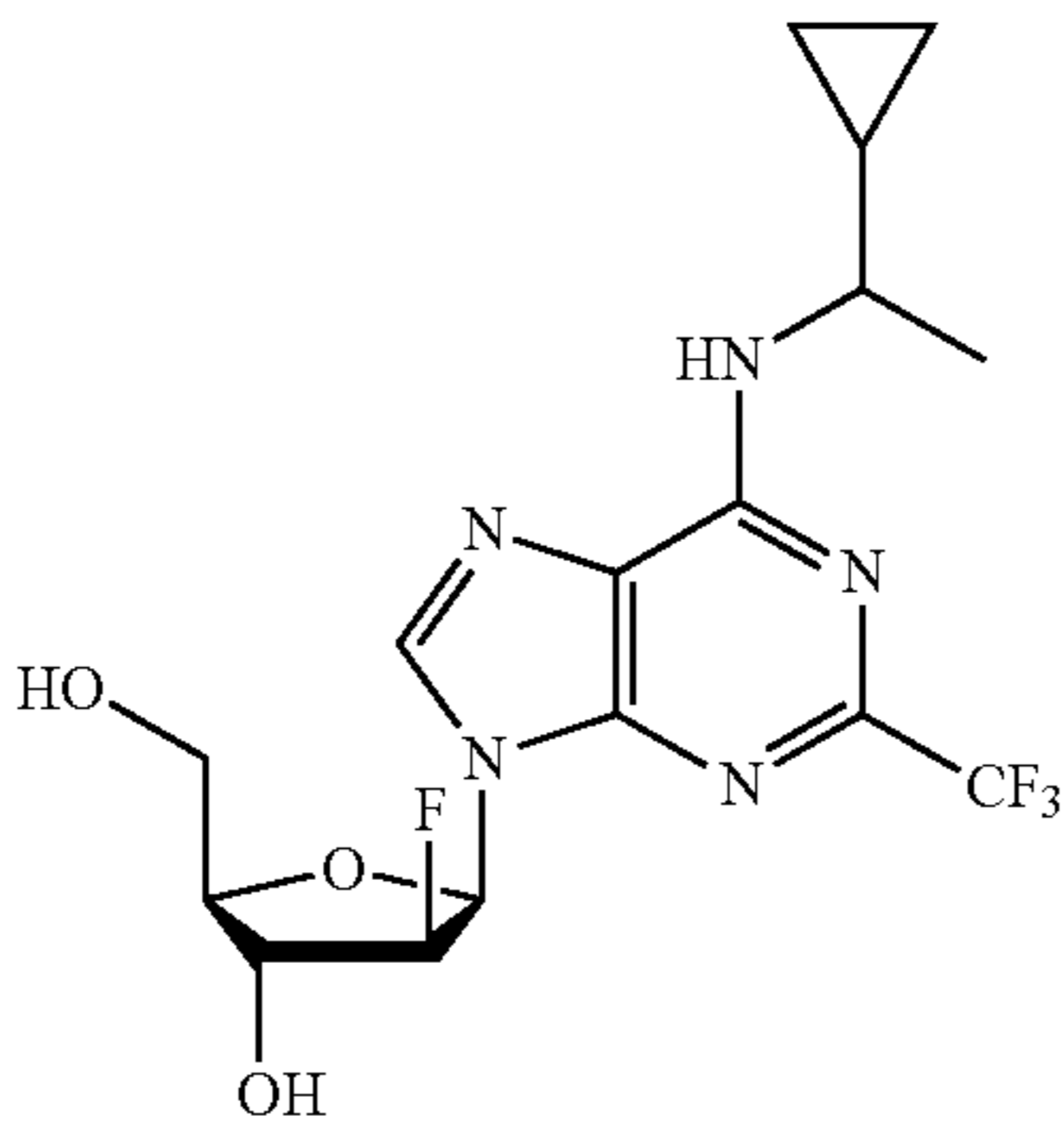
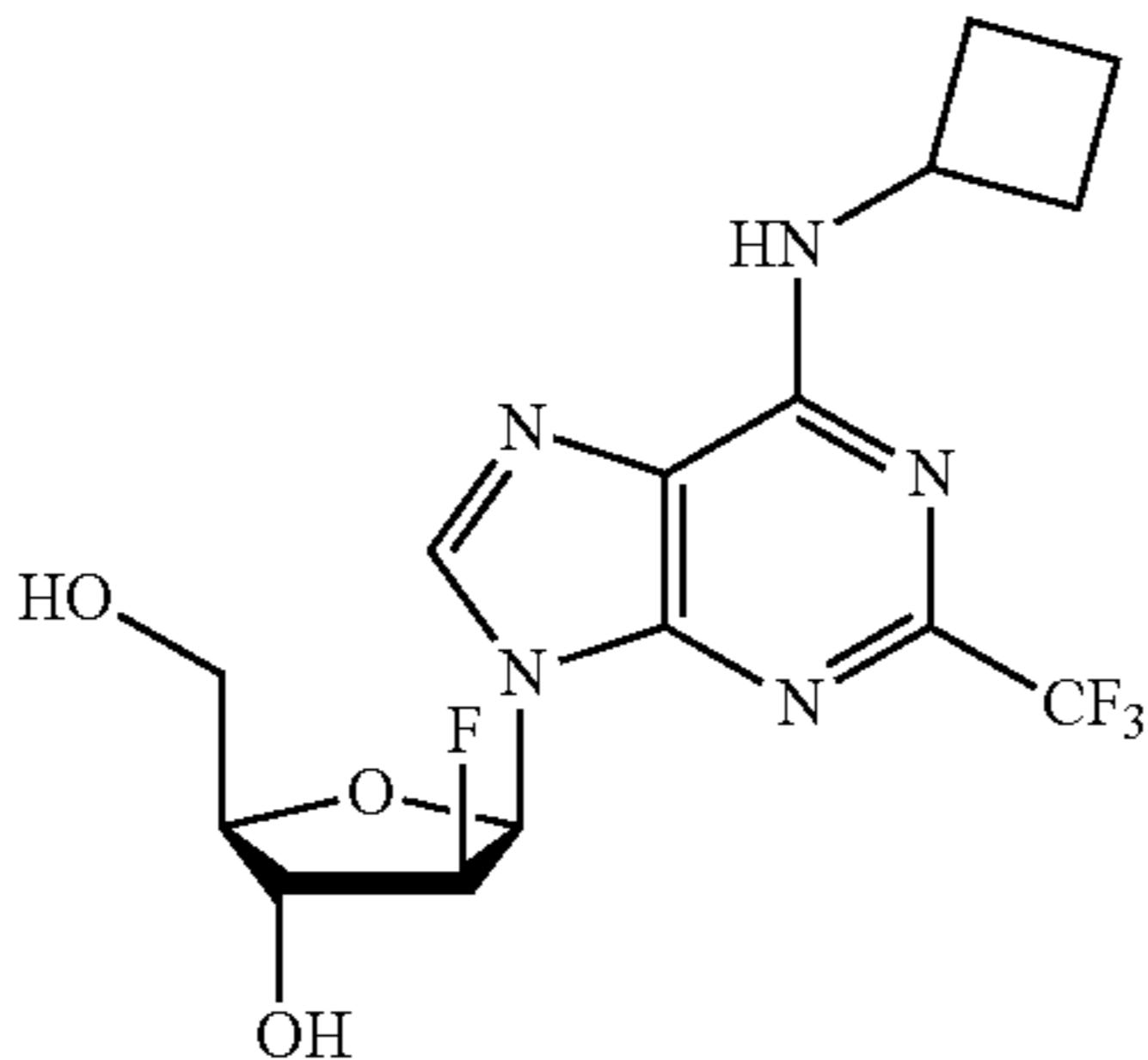
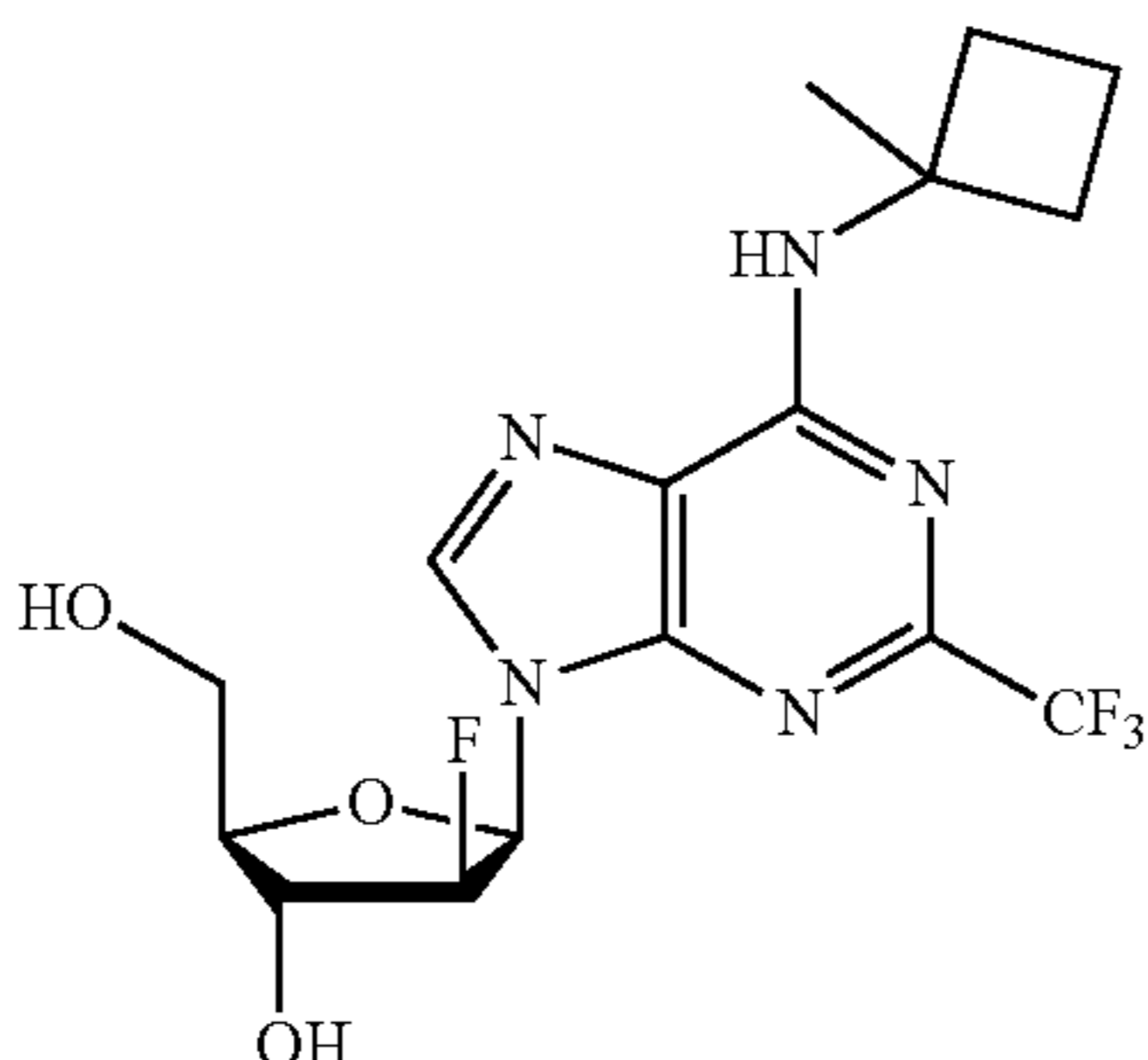
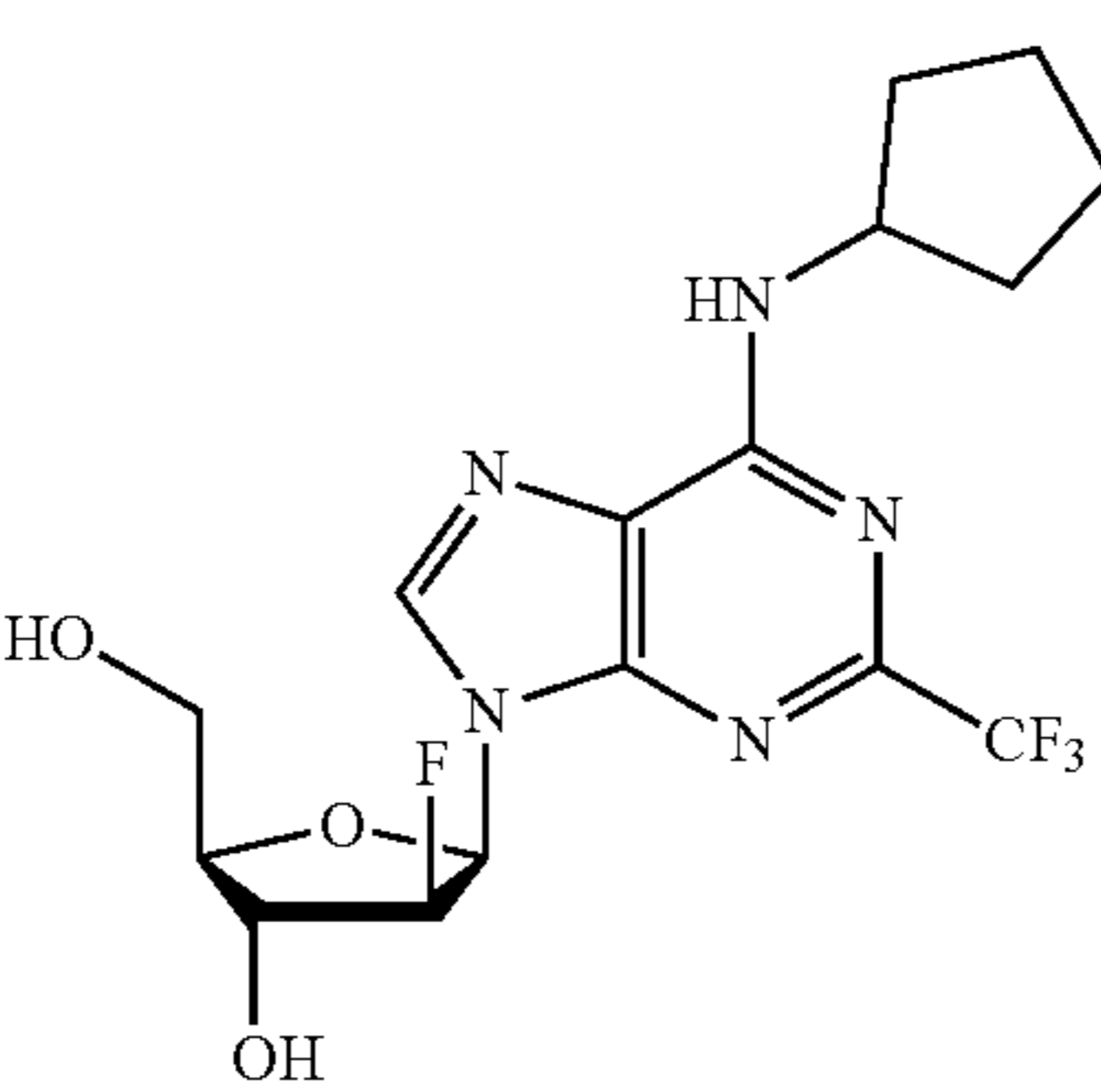
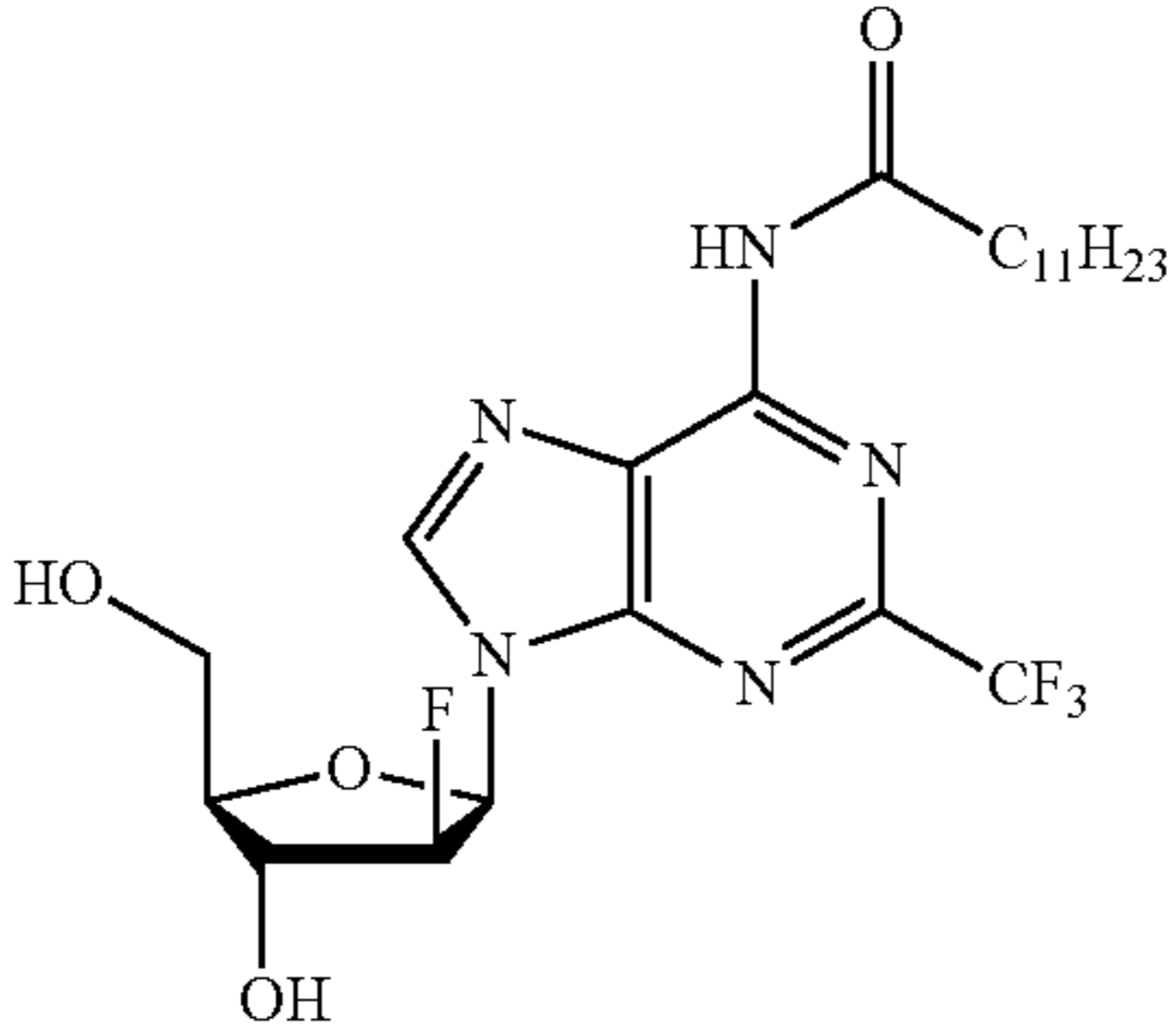
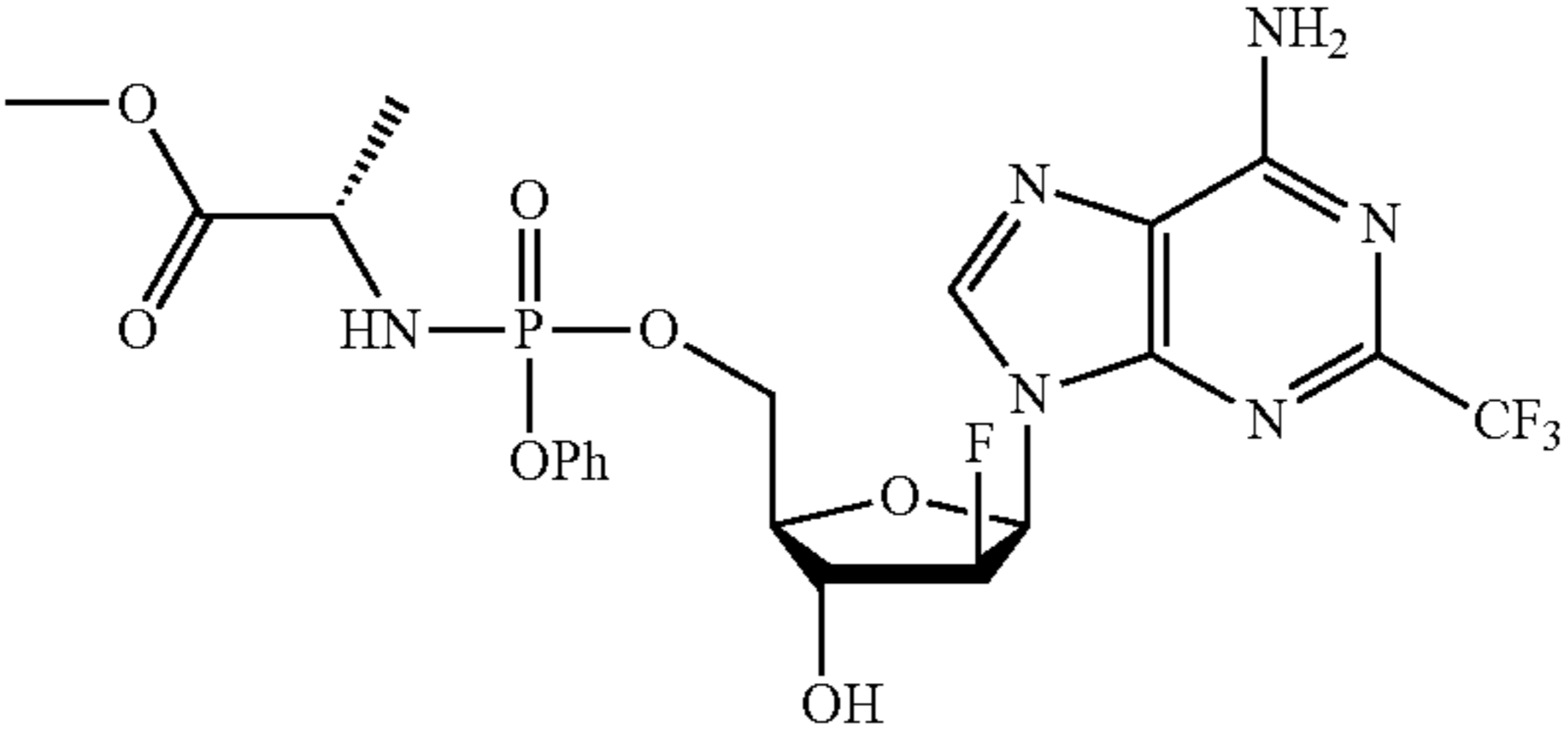
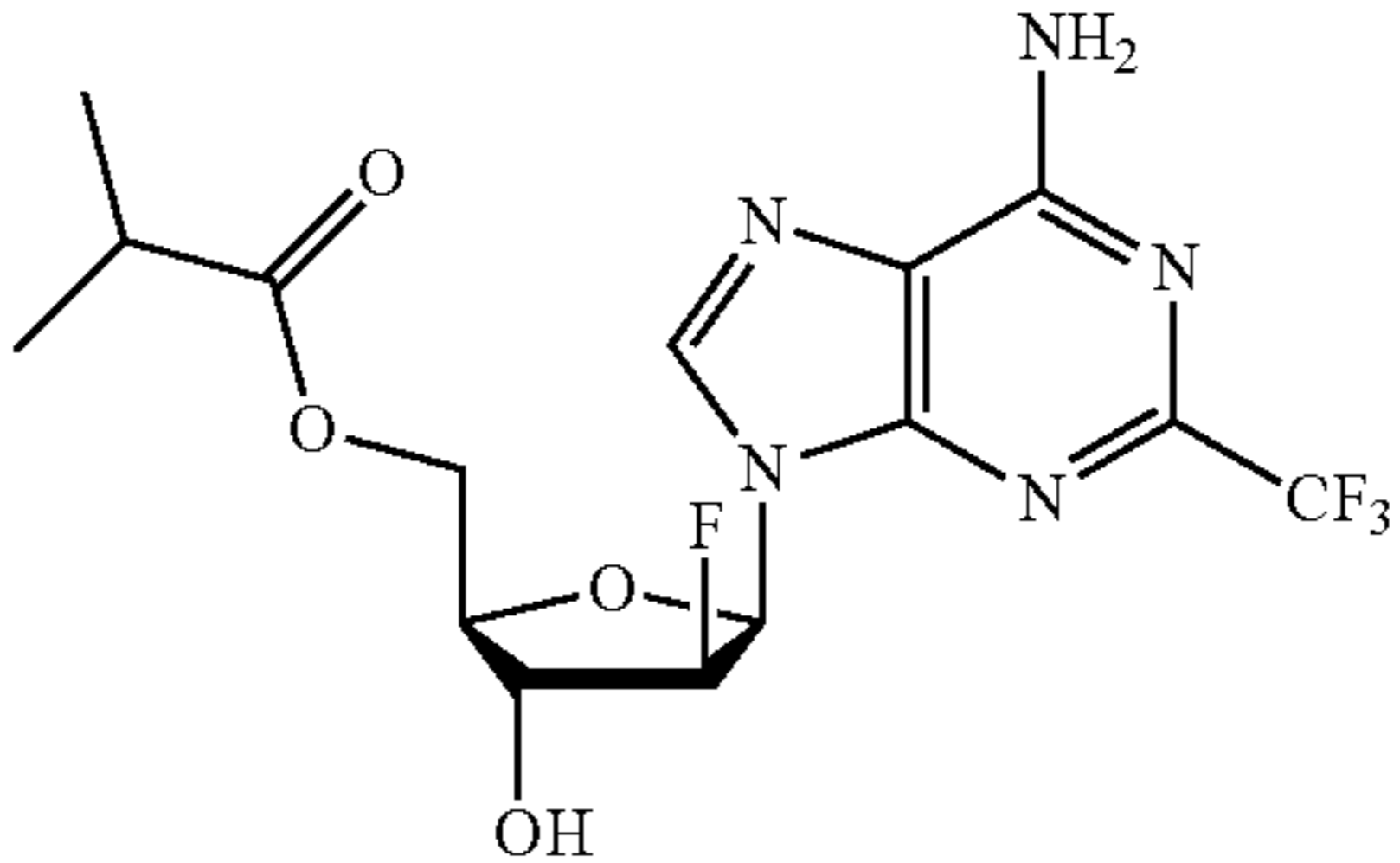
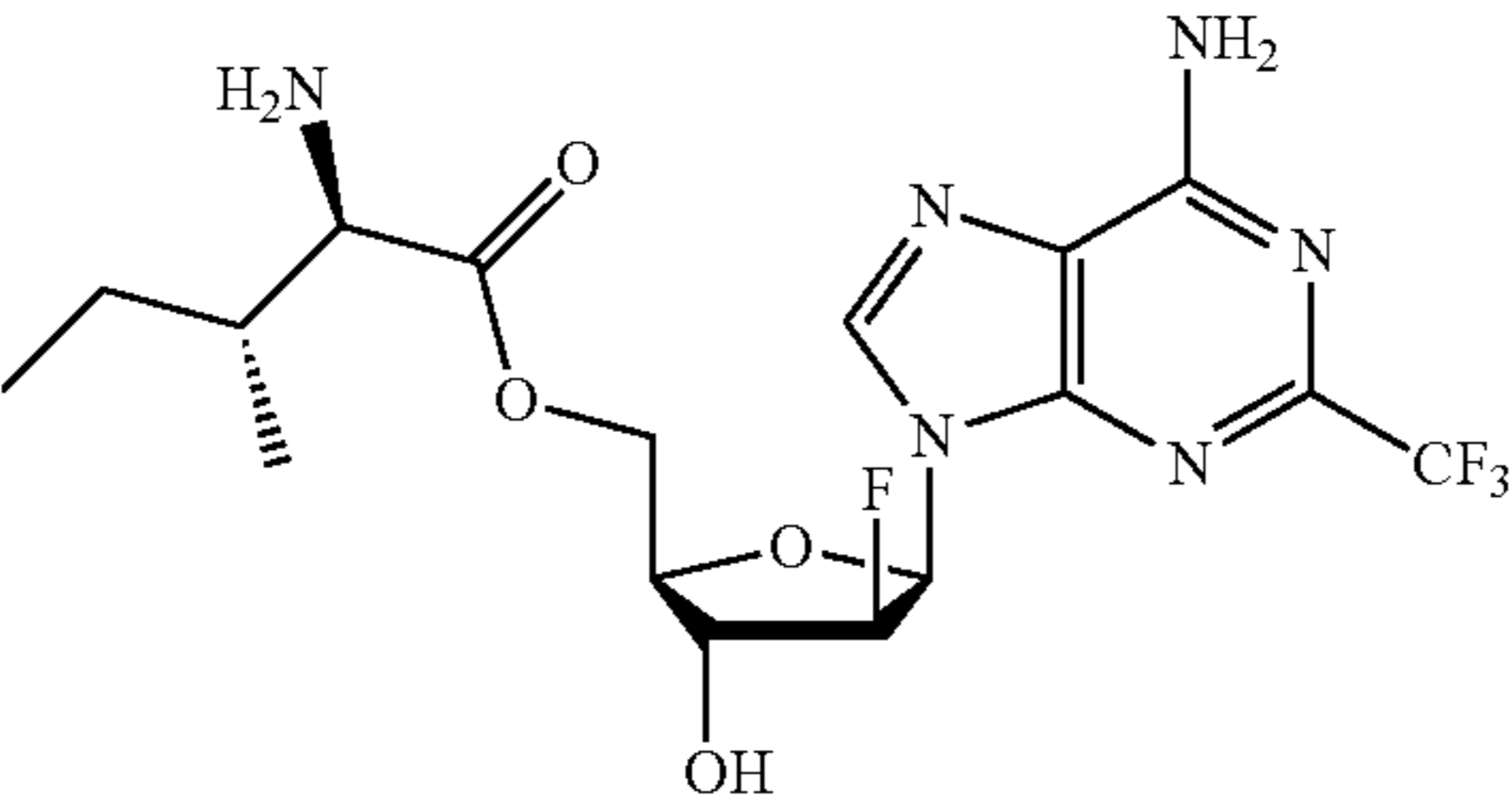
Compound	Structure	IC ₅₀ (μM)	
		MDA-MB-231	BT549
7c		2.58	Not determined
7d		20.54	15.13
7e		Not determined	13.75
7f		>50	13.54
7g		Not determined	5.89

TABLE 1-continued

Compound	Structure	IC ₅₀ (μM)	
		MDA-MB-231	BT549
10		3.19	Not determined
12		13.72	13.08
15		7.12	>50
18		11.42	>50

3. In Vivo Studies for Preliminary Safety and Efficacy in a Solid

Tumor, Triple Negative Breast Cancer Model

Athymic nude mice (CrI:Nu(NCr)-Fox^{1nu}; Charles River) were injected s.c. in the right flank with 100 μL MDA-MB-231 cells in 1:1 RPMI **1640** and Cultrex BME Type 3 (1×10⁶ cells/mouse). Tumors were allowed to grow until 500 mm³ (Tumor Volume= (4/3)π×Length×Width²), at which point mice were dosed QIDx5 for 2 weeks by intraperitoneal injection with either vehicle (N-Methyl-2-Pyrrolidone (NMP), Polyethylene glycol 400 (PEG400), and saline at a ratio of 1:2:2 v/v/v), 25 mg/kg of Clofarabine, or 25 mg/kg of compound 5. Tumor volumes were measured twice weekly, and bodyweight was measured daily during the dosing period. This was a pilot test to determine anti-tumor

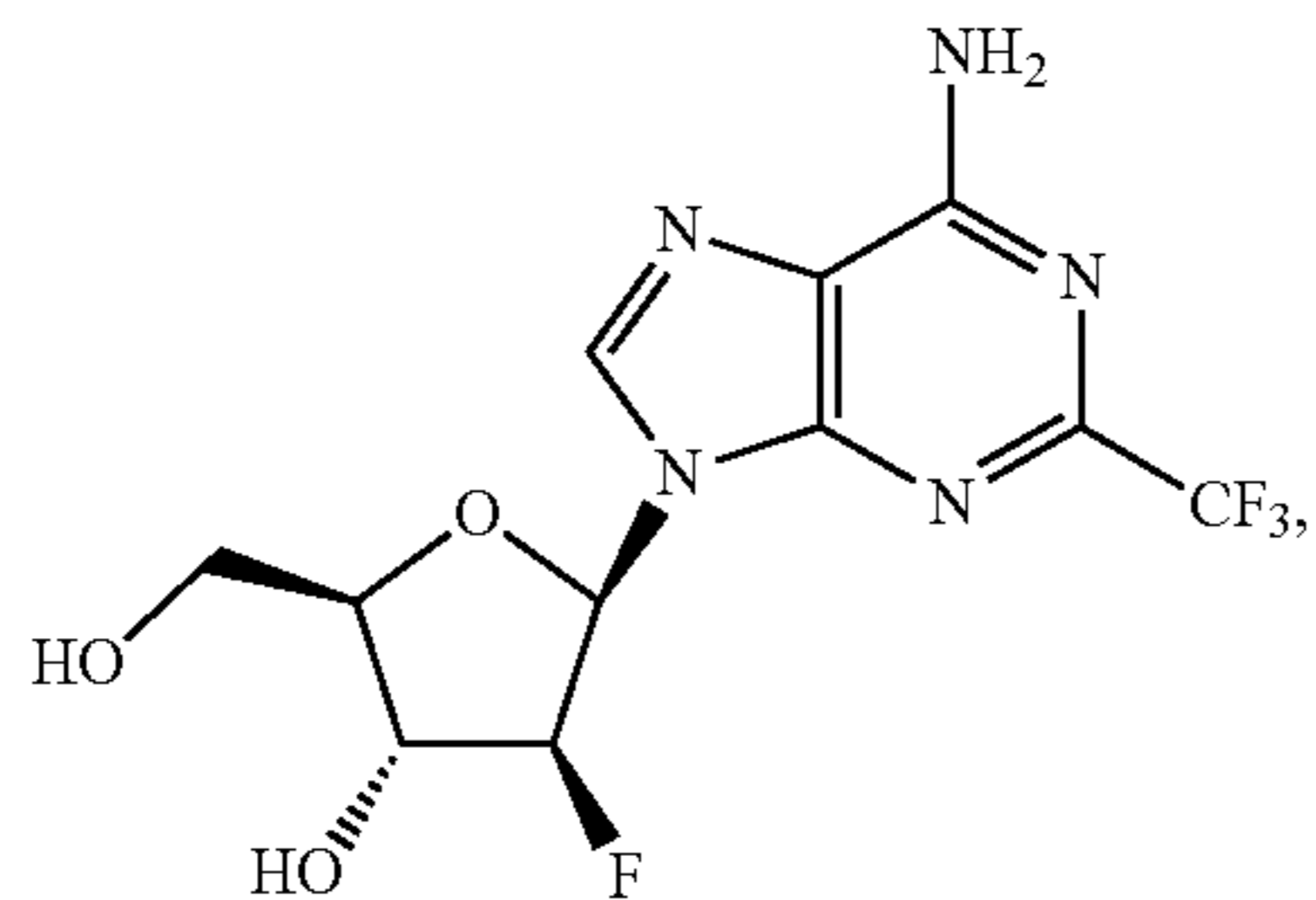
50 growth activity, so regrowth was not measured and the study was terminated two days after the final dose. The data is as shown in FIG. 1

As a result of the anti-growth efficacy of compound 5, a basic dose escalation test for tolerance of drug concentration was conducted. Briefly, a cohort of B6C3F1/N female mice were split into three dosing arms: Control (N=2), Clofarabine (N=3), and compound 5 (N=3). The dosing schedule was set based on previous and historical dosing with nucleosides, Q1Dx5 with a 2-day washout period before dose escalation. The selected dose concentrations were 25 mg/kg, 40 mg/kg, and 55 mg/kg. Blood was collected weekly by submandibular bleed for ALT and AST measurements, and at necropsy major organs were examined for gross toxicity. Toxicity was seen immediately following the 55 mg/kg dose of Clofarabine, while compound 5 treated mice survived to the end of the study. This indicates that the safety profile is improved with compound 5. The data is as shown in FIG. 2.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A compound having a structure:



or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1, and a pharmaceutically acceptable carrier.

3. A method of treating breast cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of claim 1 or a pharmaceutically acceptable salt thereof.

* * * * *